Advances in upper gastrointestinal surgery:

Management and Diagnostic techniques

Gregory L Falk

MB.BS, FRACS, FACS

Submitted in fulfilment of the requirements for the degree of Doctorate of Medical Science

School of

Medicine

Sydney

June 2023

Declaration

To the best of the candidate's knowledge, this thesis contains no material previously published by another person, except where due acknowledgement has been made.

This thesis is the candidate's own work and contains no material which has been accepted for the award of any other degree or diploma in any institution.

Human ethics

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Humans Research (2007, updated 2018). The proposed research study received human research ethics approval by serial ethics of the local institutional ethics committee of Concord Repatriation General Hospital, Sydney over many years including 2019/ETH07856, CH62/6/2011-092, 10/1/2013/.INR/12/CRGH/248,CH62/6/2012-189, LNR/12/CRGH/248.

Abstract

Upper gastrointestinal surgery has progressively moved from the surgically open abdomen to minimally invasive surgery, largely due to technological improvements in instrumentation. A direct result of this Gestalt has been improved patient comfort, rapid recovery and significantly less length of stay in the hospital and therefore significant cost-savings. This was the key impetus to my development of many of the skills in minimally invasive surgery and the subsequent dissemination to other surgeons in an organized and well-recognized teaching system. Many of the novel techniques of this type of surgery led to several publications both in the English and French oncological and gastrointestinal literature. In philosophical terms, it also led to a significant interest in gastrointestinal physiology and the setting up of a reference laboratory that led to many research publications on gastroesophageal reflux in terms of 24-hour pH/impedance and manometry. These skills also allowed the joint development and validation of a scintigraphic test for gastroesophageal reflux and its extra-oesophageal manifestations in the head, neck, and lungs. It allowed significant advances in the recognition of extra-oesophageal manifestations of reflux with the production of five PhD candidates, one of which has already been completed and two are approaching submission through the University of Notre Dame.

The implementation of minimally invasive surgery and its basis in physiological testing has spawned numerous publications that have significantly advanced upper gastrointestinal surgical outcomes which have been documented in the surgical and medical literature.

Acknowledgments

No funding was received for candidature. I wish to acknowledge long-standing colleagues for their support, proofreading, collaboration and enthusiasm, including Dr Hans Van Der Wall, Dr Leticia Burton, Mrs Teresa Larsen, Ms Suzanna Gooley and many co-authors. Particularly I wish to thank two mentors who had considerable influence on the genesis of the long-standing interest on the topic, Professor David Gillett, and Professor Brian McCoughan.

Thesis for Doctorate of Medical Science: Gregory L Falk

Table of Contents

CURRENT POSTS

Clinical Associate Professor of Surgery; University of Sydney

Senior Specialist; Department Head, Upper GI Surgery/Endosurgery

Repatriation General Hospital Concord

Visiting Medical Officer: Repatriation General Hospital Concord

Visiting Medical Officer: Sydney Adventist Hospital Wahroonga

Director: Sydney Heartburn Clinic Oesophageal Diagnostic Laboratory

MEMBERSHIPS

AHPRA – MED0001020342
GMC (London) – 3178113 (previous)

EDUCATION

Secondary	Higher School Certificate 1973
Tertiary	Sydney University 1974-1978, MBBS 1979
Postgrad	Royal Australian College of Surgeons FRACS Part 1 1982
	Royal Australian College of Surgeons FRACS Part 2 1986; Certificate 4687
	American College of Surgeons FACS 2002

SENIOR APPOINTMENTS

1988:	Clinical Superintendent: The Nepean Hospital, Penrith
1989-91:	Clinical Superintendent in Surgery: Concord Repatriation General Hospital
1989-90:	VMO: Upper Gastrointestinal Surgery/Endoscopy, Nepean Hospital, Penrith.
1990-93:	VMO: Auburn District Hospital, General Surgery
1991-pres:	VMO: CRGH, Upper Gastro-Intestinal Surgery
2003-pres:	Departmental Head, Upper GI Surgery/Endosurgery: CRGH
2003	Clinical Associate Professor of surgery, CRGH, University of Sydney

ADMINISTRATION:

Clinical superintendent: Nepean District Hospital (past)
RGH Concord (past)
Head of Department of UGI Surgery: RGHC (2003-current)

HIGHER DEGREES SUPERVISED

Dr Felix Michael Lee: *Composite repair of giant hiatus hernia* awarded Diploma of Surgical Sciences the University of Edinburgh 2021

Dr Miho Mugino: *Diagnosis of Giant Hiatus Hernia*- awarded Master of surgery University of Edinburgh

Dr Izhar-Ul Haque MBBS: *Effect of total and metastatic lymph node count, metastatic lymph node ratio, local invasion and chemotherapy on five-year survival of gastric cancer patients undergoing gastrectomy at a major Australian tertiary hospital- awarded* Master of Surgery University of Sydney 2015

Dr Garrett S Smith MBBS FRACS: *Mesh in giant hiatus hernia surgery*- awarded Master of surgery University of Sydney 2005 (with co-supervisor Prof C Martin)

Dr David Rangiah MBBS FRACS**:** *Laryngo-pharyngeal reflux and gastro-oesophageal reflux: a comparative quality of life study after laparoscopic fundoplication*- awarded Master of Surgery Sydney University 2007

Ms Leticia Burton: *New applications of nuclear scintigraphy in the diagnosis and management of GORD*- awarded *PhD* University of Notre Dame 2021

Dr Miho Mugino – *Giant Hiatal hernia (GHH) and Gastric Volvulus (GV): Diagnostic Accuracy of gastroscopy and barium study* -current PhD candidate University of Notre Dame Sydney

Dr Jin-Soon Park – *Diagnosis and therapy in oesophago-gastric disease*- current PhD candidate University of Notre Dame Sydney

Dr Oleksandr Khoma – *Reflux aspiration, Natural History, Pathophysiology, Clinical Presentation and Treatment Outcomes- current PhD candidate University of Notre Dame Sydney*

Dr Dulani Goonawardhana- The Pulmonary sequalae of gastro-oesophageal reflux disease. Current master's candidate University of Notre Dame Sydney

Introduction

My current role is the chairman of a major teaching hospital surgical department training multiple national, ANGOSA and international post fellowship trainees, guiding clinical research, and pursuing clinical research in techniques of investigation of typical and atypical reflux disease. I have had innovative involvement in the curative management of oesophageal cancer and development of minimally invasive techniques of surgery.

During surgical training my initial interest in investigation of surgical diseases led to pursuit of a year of research, I was awarded the Mitchell Crouch fellowship of the RACS, to allow laboratory research in animals investigating platelet functionality with vascular turbulence using radioactive indium. This work was innovative and led to several presentations and publication and an award from the vascular surgical society of Australia. I finished my surgical training and followed this translational research with a more practical area of innovation in the surgical treatment of complex duodenal ulceration. This area also had a physiological background in the study of the secretion of acid moderated by neural mechanism and gastrointestinal hormones, and mucosal resistance which were very much integral to the clinical management.

My experience in clinical problem solving often stimulated worthwhile questions and there followed a varied contribution where current management allowed a potentially improved alternative approach to be evaluated.

The previously undifferentiated course of surgical training became more focused in later years of post-fellowship training becoming more involved in upper gastrointestinal disease. Overseas experience followed with time spent in oesophagogastric units. I travelled to the East Birmingham Chest Hospital gaining oesophageal physiological training in the laboratory and visiting with Prof Hugo Matthews a world-renowned oesophageal surgeon. I trained in North Staffordshire with colleagues of Prof Ronald Belsey and learned his world recognised techniques of antireflux surgery which were at the forefront of management during those years. I travelled via America to the influential service of Prof Tom DeMeester

who was then in Creighton University, Omaha, in a very well recognised oesophagogastric centre, as head of Department. He was later to become the senior professor at the University of California, Los Angeles. He co-developed the remarkable techniques of 24-hour pH reflux study which became the world recognised diagnostic test for standard reflux disease. I continued to pursue this substantive Interest in oesophageal physiology and surgery of the oesophagus and cardio-oesophageal junction.

With appointment to a consultant position of surgery and a responsibility for oesophagogastric surgery and the cardio-oesophageal junction and associated surgical endoscopy, it became my full time remit at the Repatriation Gen Hospital Concord in 1988. I established several surgical centres for interventional endoscopy in a number of major teaching hospitals in Sydney during this period, and was instrumental in the development in major centres in the country. I introduced laser endoscopy to Sydney and for many years re-canalised malignant oesophageal disease as the primary palliative treatment of patients with oesophageal obstruction from malignancy. This was not performed any where else in Sydney.

A revolution in understanding of the causation of upper gastrointestinal diseases occurred during this time, and also revolutionary technological advances in surgery during the late 80s. The development of antisecretory medication and an awareness that duodenal ulceration was an infective disease which could be managed by antibiotics rather than surgery occurred. Laparoscopy was introduced and I was at the forefront of innovative techniques and teaching in this area for many years until it became mainstream. I ran the Sydney advanced laparoscopic training (SALT) course between 2003 and 2007, the only such facility in Australia and attracted young surgeons nationwide for the three, week-long sessions, each year.

I pursued multiple techniques of innovation in both open and minimally invasive surgery over the years with a focus on the development of hiatal (oesophago-gastric) surgery with antireflux therapy, giant hiatus hernia repair, and diagnosis of oesophageal diseases both benign and malignant.

This was facilitated by the long-standing surgical oesophageal laboratory which I established for the management of oesophageal disease and reflux very early in my career on returning from the UK. This was later to be invaluable in the management of atypical symptomatology of reflux and integral to the development of nuclear medical testing which identified extra-oesophageal reflux and pulmonary, diseases associated with reflux events. I became head of my hospital department of upper gastrointestinal surgery in 2003 and was awarded the title of clinical associate Professor for research and teaching at that time. Both through teaching and publication, this work influenced many surgeons nationally and internationally.

In cooperation with my colleague Prof Hans Van Der Wall, we established and validated a testing regimen which has become a major focus of research, which demonstrated hitherto unrecognised extra-oesophageal disease (although suspected) associated with the regurgitation events becoming extra oesophageal (so called atypical reflux disease). The understanding of the physiology of this situation evolved with thorough investigation and it became demonstrably evident that there was a major motility component in the genesis of symptoms and complications of the diseases. it was also seen that appreciation of the extent of the reflux event has implications for sinus disease, pulmonary disease, and laryngopharyngeal symptoms. The testing program utilised modern nuclear medicine technology of hybrid gamma camera and SPECT scanning to localise gastric isotope refluxing into pharynx and larynx, sinuses, lung and even eustachian tubes. This was validated against standard oesophageal physiological techniques in my laboratory, and against surgical treatment. Normal values were obtained. This work was enthusiastically received by members of the respiratory, ear nose and throat and gastroenterological community internationally. The ramifications for a new understanding of multiple different diseases previously not evident although long suspected but were positively diagnosed by this technique. The commencement of the program to has allowed the appreciation of the cause of disease in different areas in respiratory medicine, ear, nose and throat and gastroenterology and will require the

development of new concepts and new treatments. There is increasing interest from multiple centers around the world.

DEFINITIVE IMPROVED DUODENAL ULCER SURGERY: HIGHLY SELECTIVE VAGOTOMY IN THE TREATMENT OF ACUTE COMPLICATIONS

Duodenal ulcer was a substantial problem in society for hundreds of years. There was a large workload managing perforation of the duodenum and lethal bleeding events as well as chronic disease and pain requiring extensive hospitalisation in a substantial proportion of the population. Surgery was performed frequently and was one of the most common operations in my early years as a surgeon. Considerable physiological research was carried out in the understanding of vagal nerve innervation of acid secretion and gastrointestinal hormonal research in the genesis of ulcer disease by surgeons, with a view to management of this disease. Management at often required removal of parts of the stomach (gastrectomy) or division of the vagus nerve to reduce acid secretion. This had consequences of attendant complications and longer-term symptomatic sequelae. The highly selective vagotomy technique was developed as it had less quality-of-life implications and controlled ulcer disease. Patients undergoing emergency surgery, however, were often treated with old-fashioned complicated surgery with major long-term sequelae. The group I worked with develop techniques of utilising highly selective vagotomy in the acute situation offering good control of ulcer disease with minimal longer term side effect.

Before demonstrating the efficacy of HSV in the acute management of duodenal complications patients were often subject to long-term lifestyle quality of life downside following a truncal vagotomy or gastric resection which were substantial. The development and popularisation of the better-quality technique of HSV allowed patients cure of duodenal ulcer in a high proportion, but minimal side effects. Publication and repeated presentation on the national stage was instrumental in changing the practice of the management of complications of duodenal ulcer to the patient's advantage in the longer term. Following use of these techniques for a decade or more, antisecretory drugs and identification of the causal effect of Helicobacter pylori allowing antibiotic therapy, replaced these techniques.

References:

1. Brancatisano R, Falk GL, Hollinshead JW, Gillet DJ. Bleeding duodenal ulceration: the results of emergency treatment with highly selective vagotomy. Aust N Z J Surg. 1992;62(9):725-8.

2. Falk GL, Hollinshead JW, Gillett DJ. Highly selective vagotomy in the treatment of complicated duodenal ulcer. Med J Aust. 1990;152(11):574-6.

Ausr. N.Z. J. Surg. 1992, **62,** 725-728

BLEEDING DUODENAL ULCERATION: THE RESULTS OF EMERGENCY TREATMENT WITH HIGHLY SELECTIVE VAGOTOMY

R. BRANCATISANO, **G. L.** FALK, **J. W.** HOLLINSHEAD AND **D. J.** GILLET

G. *I. Unit, Department of Surgery, Concord Hospital, Concord, New South Wales, Australia*

We report the results of a prospective study of all patients undergoing highly selective vagotomy (HSY) for bleeding duodenal ulceration (BOU) at Concord Hospital between 1979 and 1989. Highly selective vagotomy was undertaken in 63 patients (58 male, 5 female) with a median age of 69 years (range: 16-89). Fifty-five patients were reviewed, 7 patients having died in the peri-operative period and one being lost to follow-up. The mean period to review was 50 months (range: 1-120). Thirty-six patients have been followed-up for more than 24 months.

Thirty-day postoperative mortality was 11 % (7 patients). Combined major and minor morbidity was 41% . Postoperative rebleeding occurred in four patients (6.3%), three of whom died. Ulceration had recurred in two of 55 patients (4%). Symptoms have been evaluated in 55 patients since operation and 93% have been graded as Visick I or II.

We conclude that HSY is effective in the emergency treatment of BOU and has few long-term sequelae.

Key words: bleeding duodenal ulcer, highly selective vagotomy.

Introduction

Highly selective vagotomy **(HSY)** is widely accept- ed as the treatment of uncomplicated duodenal ul- cer (DU) because of its low mortality and minimal operative sequelae. [1-5] It has largely replaced trun- cal vagotomy and drainage. [6-8] The use of HSY in the treatment of DU complicated by bleeding is less well established. Johnston *et al.* recommended the use of HSY for bleeding duodenal ulcers (BDU) in 1973 to prevent the sequelae of truncal vagoto- my.[9,10] Good early results using HSY for bleeding duodenal ulcers in small series of patients have been reported. [11-15]

At Concord Hospital, HSY has been shown to be an effective procedure in the elective treatment of intractable DU.[3] Encouraged by these results, the use of HSY in the emergency treatment of bleeding duodenal ulcers was adopted. This paper reports our medium-term experience with HSY in this situation.

Methods

A prospective record of all patients undergoing HSY for BDU at Concord Hospital was kept from 1979 onwards. It has been the Unit policy since 1981 that all patients with BDU, without historyof gastric ulcer, should undergo **HSY** as definitive treatment at the time of surgery for bleeding. Patients reported in this study since 1981 have therefore been consecutive and unselected.

Indications for surgery, associated illnesses and postoperative complications were recorded on a proforma for computer analysis. A pre-operative illness rating for each patient was calculated from data on the proforma. The presence of shock and disease within an organ system was arbitrarily scored as one, and the total number was considered the pre-operative 'illness score' of that patient.

The patients were divided into two groups, depending on the reason for admission to hospital: Type A patients were those admitted with a bleed- ing DU; and Type B patients were those admitted with another illness who developed a bleeding DU during the admission.

A standardized technique of highly selective va- gotomy was performed on all patients. The ulcer base was oversewn in all patients through a duoden- otomy or pyloroduodenotomy. Our policy was to operate for bleeding when there was haemodynamic instability, when the 4 unit transfusion threshold was exceeded, or significant recurrent or continued haemorrhage occurred.

The patients were reviewed (by R. B.) and as- signed a symptom score as modified by Goligher *et* a/. [16] Patients who died after the last review were assigned a symptom score at time of last review. If the results were indeterminate, the local medical

Correspondence: Mr G. Falk FRACS, 2nd Floor Clinic, Department of Surgery, Concord Hospital, Concord, NSW 2139, **Australia.**

Accepted for publication 19 March 1992.

officer and family were interviewed and a grading made. Patients whose symptoms were suggestive of ulcer recurrence were submitted to endoscopy.

Results

Highly selective vagotomy for BDU was performed on 63 patients (58 male, 5 female) with a median age of 69 years (range: 19-89). Fifty-two patients (type A) were admitted because of a BDU. Eleven patients (type B) were admitted with another illness

which became complicated by a BDU while in hospital. Routine approach to the ulcer bed was througha duodenotomy, but four cases required a pyloroduodenotomy for access, which was reconstituted longitudinally. Accompanying outlet obstruction was treated by duodenoplasty or pyloroplasty in eight patients, and gastroenterostomy in one patient.

MORTALITY

Type A patients had a mean pre-operative illness score of 1.6 and a mean age of 62 years. The 30 day mortality rate in this group was 3.8%. Type B patients had an illness score of 4.0 ($P < 0.05$), a mean age of 71 years and a 30 day mortality rate of 45%. The cumulative 30 day mortality rate for type A and B patients was 11% (7 patients). The mean age, coincident diseases and mortality rates of each group are presented in Table I.

REBLEEDING

Early rebleeding occurred in 6.3% of cases (4 patients), three of whom died. Two patients succumbed prior to re-operation due to multi-organ failure. A Polya gastrectomy was performed on the other two patients, with one death from multi-organ failure. Major and minor complications occurred in 41% of patients.

REVIEW

Fifty-five patients were reviewed. The mean period of follow-up was 50 months (range: 1-120). Thirty-six patients (65%) have been reviewed for more than 24 months. In the period since last

Table L Pre-operative risk factors: Mortality

	No. patients	Mean age (Years)	Mean pre-op. illness score	Mortality% (30 days)
Type A*	52	62	1.6	3.8
Type Bt	11	71	4.0	45

$P < 0.05$, Chi-squared lest.
*BDU only.
tBDU in hospital.

Table 2. Postoperative symptom scoring

Visick grade	Patients No.	<1/o	Patient satisfaction
1	38	70	Excellent (93%)
2	13	23	
3	2	3.5	Unsatisfactory (7%)
4	2	3.5	

Table 3. Sequelae of HSY

Symptom	No.
Major	
Recurrence	2
Diarrhoea	
Dyspepsia	
Minor*	
Fullness	11
Dyspepsia	5
Dumping	1
Flatulence	I
Regurgitation	

***On direct questioning.**

review 14 patients had died of unrelated causes. Recurrent ulceration has occurred in two patients (4%). A further six have had mild dyspepsia with no ulceration on endoscopy. Fifty-one of the 55 patients reviewed (93%) had an excellent sympto- matic outcome (Table 2). Unsatisfactory modified Visick gradings were assigned to patients with per- sistent dyspeptic symptoms or troublesome diarr- hoea **(III)** or those with proven ulcer recurrence (IV). The main sequelae following HSY are listed in Table 3. Early post-prandial epigastric fullness occurred in 11 patients and was easily resolved by minor dietary adjustment in all cases. It was only detected by direct questioning.

Discussion

Although Johnston *et al.* advocated the use of HSY for selected cases of BDU in 1973[9] it has not been widely adopted as routine emergency therapy.[1,0,11,17,18] Truncal vagotomy and drainage has remained the procedure most commonly practised.[17] It has low rates of mortality, rebleeding and ulcer recurrence-,[6,8,20,25] but a higher incidence of vagotomy-induced diarrhoea and dumping. As reported by Miller *et al.* (unpubl. data) and others, these symptoms occur in 5-25% of patients treated by TVD_6.l6,21,22

MORTALITY

An overall mortality rate of 11% as achieved with the use of HSY is comparable with the mortality

rates experienced by other authors performing TYD. Mortality rates have been reported between 2.5 and 20%.[20,23-29]

There have been a few reports of HSY used in treatment of BDU in the recent English-language surgical literature, detailing a total of 114 patients.[9,13,17,18] The combined 30 day mortality rate of these series is 3%. Such a low mortality has been achieved by careful patient selection and exclusion of all patients of advanced age (combined mean age: 51 years). By contrast, this series is predominantly aged (mean: 69 years) and has a high rate of intercurrent illnesses.

In this series, the risk of death following surgery was shown to be low (3.8%) in type A patients and high (45%) in type B patients. The proportion of each type within a given series influences overall rates of mortality. Similarly, the presence of other illnesses and of increasing age have been shown by Pimpl *et a /.* [29] and others[19,20,31,34] to be causes of increased mortality. Adoption of a 'unit' policy with *uniform attitudes to early management* has been effective in lowering mortality.[36]

REBLEEDING

The rate of rebleeding following HSY and oversew of BDU is similar to the rates reported (4-10%) for TYD.[20,25,36]

RECURRENCE

Ulcers have recurred in two patients (4%) after a mean period of follow-up of 50 months. This rate is similar to the experience of this unit in the elective treatment of DU, where recurrence occurred in 5.3% of patients.[3] It has been generally reported that most ulcers recur within 2 years after surgery,[37-39] but others report an increasing incidence of recurrent ulceration with time.[41] Recurrence rates of TVD have been reported as varying between 2 and 15%.[20,22] We believe that the 4% recurrence rate reported is comparable with rates reported following TYO.

SYMPTOMATIC OUTCOME

Ninety-three per cent of patients in this series had an acceptable outcome on review - no different from the elective results reported by Hollinshead *et a/.* [3] This contrasts with reports of TYD in which post-truncal vagotomy diarrhoea and dumping was a considerable problem in upwards of 20% of patients.[6,16,21,22] It is evident that HSY is as effective as TVD in urgent situations, but eliminates post-vagotomy symptoms almost entirely.

Conclusions

The following conclusions were reached:

- Highly selective vagotomy is as effective as TVD in the emergency treatment of bleeding duodenal ulcer. but has significantly fewer long-term sequelae.
- Highly selective vagotomy is the preferred option for emergency treatment of bleeding duodenal ulcer, in Group A type patients.
- Mortality rates are high in patients for whom bleeding ulcer complicates hospitalization for another illness.

References

1. GouGHER J.C., HILLS G. L., KENNY T. E. & Nurrrn E. (1978) Proximal gastric vagotomy without drain- age for duodenal ulcer: Results after 5-8 years. *Br. J. Surg.* **65,** 145-51.
2. AMDRUP E. (1983) Vagotomy *lnt. Surg.* **68,** 293-4.
3. Hou.1NSHEAD J. W.. SMITH R. C. & GILLETT D. J. (1982) Parietal cell vagotomy: Experience with 114 patients with prepyloric or duodenal ulcer. *World J. Surg.* **6,** 596-602.
4. AMDRUP E., ANDERSON D. & HosrnuP H. (1978) The Aarhus County vagotomy trial: I. An interim report on primary results and incidence of sequelae follow- ing parietal cell vagotomy and selective gastric vagotomy in 748 patients. *World J. Surg.* 2. 85-90.
5. JoHNSON D. (1975) Operative mortality and post-operative morbidity of highly selective vagotomy. *Br. Med. J.* **4.** 545-7.
6. STODDARD C. J., JoHNSON A. G. & DUTHIE H. L. (1984) The four to eight year results of the Sheffield trial of elective duodenal ulcer surgery: High selec- tive or truncal vagotomy" *Br. J. Surg.* **71,** 779-82.
7. HOFFMAN J .. JENSEN H. E.• SCHULLE S.. POULSEN P. E.& CHRISTIANSEN J. (1984) Prospective controlled va-gotomy trial for duodenal ulcer: Results after five years. *Br. J. Surg.* **71,** 582-5.
8. STABILE B. E. & PASSARO E. (1984) Duodenal ulcer: A disease in evolution. *Current Problems in Surgen-* **21.**
9. JoHNSTON D.. LYNDON P. J.. S,11TH R. B. & HntPHREY C. S. (1973) Highly selective vagotomy without drainage procedure in the treatment of haemorrhage. perforation and pyloric stenosis due to peptic ulcer. *Br. J. Surg.* **60.** 790-6.
10. JoHNSTON *D.* (1977) Division and repair of the sphincteric mechanism at the gastric outlet in emer-gency operation for bleeding peptic ulcers. A new technique for use in combination with suture ligationof the bleeding point and highly selective vagotomy. *Ann. Surg.* **186.** 723-9.
11. HoAK B. A.. TILEY E.. Kcs,11NsKu R. & BOLAND J. P. (1 988) Parietal cell vagotomy for bleeding duodenal ulcers. *Am. Surg.* **SA,** 249-52.
12. GOREY T., LENNON F. & HEFFERNAN S. (1984) Highly selective vagotomy in duodenal ulceration and its complications. *Ann. Surg.* **200,** 181-4.
13. KNIGHT C. D.. VAN HEERDcN J. A. & KELLY K. A. (1 983) Proximal gastric vagotomy. *Ann. Surg.* **197.** 22-6.
14. FALK G. L., HOLLINSHEAD J. W. & GILLETT *D.* L. (1 990) Highly selective vagotomy in the treatment of complicated duodenal ulcer. *Med. J. Aust.* **152,**574-6.

15. HOFFMAN J., DEVANTIER A., KoELLt T., JENSEN A. E.(1967) Parietal cell vagotomy as an emergency procedure for bleeding peptic ulcers. *Ann. Surg.* **206,** 583-5.
16. GouGHER J.C., PuLVERTAFT C. N., IRVIN T. T. *et al.* (1972) Five to eight years results of truncal vagotomy and pyloroplasty for duodenal ulcer. *Br. Med. J.* **1,** 7-13.
17. HENDENSTEDT S. & LUNDQUIST G. (1978) Selective proximal vagotomy as an emergency and definitive operation for massive ulcerous bleeding. *Acta Chir. Scand.* **144,** 241-8.
18. Ross, R. L., DIAL P. F. & GEORGI B. (1986) A five to ten year follow-up study of parietal cell vagotomy. *Surg. Gynecol. Obstet.* **162,** 301-6.
19. HUNT P. S. (1986) *Castro-Intestinal Haemorrhage.* Churchill Livingstone.
20. HUNT P. S. (1986) Bleeding ulcer: Timing and technique of surgical management. *Aust. N.Z. J. Surg.* **56,** 25-30.
21. GoLJGIIER J. C., PuLCERTAFT C. N., DEDOMBAL F. **T.** *et al.* (1968) Clinical comparison of vagotomy and pyloroplasty with other forms of elective surgery for duodenal ulcer. *Br. Med. J.* **2,** 787-9.
22. KENNEDY T., CONNELL A. **M.,** LOVE A. H. G., MACRAE K. D. & ANNE SPENCER E. F. (1973) Selective or truncal vagotomy? Five-year results of a dou- ble blind, randomised, controlled trial. *Br. J. Surg.* **60,** 944-8.
23. BAMBACH C. P., CouPLAND G. A. E. & Cw.1BERLAND V. **H.** (1976) Haematemesis and melaena. Surgical management. *Aust. N.Z. J. Surg.* **46,** l07-12.
24. SCH!LLOR K. F. R., TRUELOVE S. C. & WILLIAMS D. (1970) Haematemesis and melaena with special reference to factors influencing outcome. *Br. Med. J.* **1.** 7-14.
25. SNYDER J. R. & STELLAR A. C. (I 968) Results from emergency surgery for massively bleeding duodenal ulcer. *Am. J. Surg.* **116,** 170-5.
26. KANG J. Y. & PIPER D. W. (1980) Improvement of mortality rates in bleeding peptic ulcer. *Med. J. Aust.* **1.** 213-15.
27. YAJKO R. D.. NORTON L. W. & EISMAN B. (1975) Current management of upper intestinal haemorrhage. *Ann. Surg.* **181,** 474-80.
28. HARDY **K.** G. (1971) Haematemesis and melaena. *Med. J. Aust.* **1,** 785-7.
29. HiMAL H. S., PERRAULT C. & MzABI R. (1978) Upper gastrointestinal haemorrhage. Aggressive manage- ment decreases mortality. *Surgery* **84,** 448-52.
30. PIMPL W., BoECKL 0., WAC!.AW!CZEKI & HEINERMAN M. (1987) Estimation of mortality rates of patients with severe gastrointestinal haemorrhage with the aid of a new scoring system. *Endoscopy* **19,** 101-6.
31. KIM B., HASTINGS K. W., BoRDAN D., FIELDING L. P. & SwANEY R. (1982) Risk of surgery for upper gastrointestinal haemorrhage. 1972 versus 1982. *Am. J. Surg.* **149,** 474-6.
32. LARSON G., SrnMIDTT, Gon J., BoND S., O'CoNNOR C. A. & R1cHAROON, J. D. (1986) Upper gastrointestinal bleeding. Predictors of outcome. *Surgery* **100,** 765-73.
33. THORNE F. L. & NYHUS L. M. (1965) Treatment of massive upper intestinal haemorrhage. A ten year review. *Am. Surg.* **31,** 413-19.
34. FARRIS J. M. & SMITH G. K. (1967) Appraisal of the long-term results of vagotomy and pyloroplasty in I 00 patients with bleeding duodenal ulcers. *Ann. Surg.* **166,** 630-9.
35. HuNT P. S., KoRMAN M. & HANZKI J. (1979) Bleed- ing duodenal ulcer. Reduction in mortality with a planned approach. *Br. J. Surg.* **66,** 633-5.
36. JoHNSTON D. & BLACK TT **R.** (1987) Recurrent peptic ulcers. *World J. Surg.* **11,** 274-82.
37. HERRINGTON L. J., DAVIDSON J. & Sm: IVAY S. J. (1986) Proximal gastric vagotomy. *Ann. Surg.* **204,** 108-13.
38. BARON **J. H.,** Wi!.LIA:11S **J. A.,** ALLGOWER **M.,** Mt;I.I.ER C. & S?ENC'ER (1982) *Vagotomy in Modern Surgical Practice.* Butterworths.
39. HOFFMAN J., OLESEN A. & h.NSEN **E.** (1987) Prospective 14 to 18 year follow-up after parietal cell vagotomy. *Br. J. Surg.* **74** 1056-9.
40. WARA **P.,** BERG V. & AMDRUP E. (1983) Factors influencing mortality in patients with bleeding ulcer. Review of seven years experience preceding therapeutic endoscopy. *Acta Chir. Scan.* **149.** 775-85.

Highly selective vagotomy in the treatment of complicated duodenal ulcer

Gregory L Falk, John W Hollinshead and David J Gillett

ABSTRACT Highly selective vagotomy has been utilized urgently in 33 patients with bleeding duodenal ulcer, 16 patients with pyloric stenosis and six patients presenting with perforated ulcer. Five patients died after surgery for bleeding duodenal ulcer, and two patients rebled after surgery. Forty-eight patients were reviewed at a mean of 28 months with an excellent outcome being obtained in 45 patients. Two of the three patients with poor results had proven ulcer recurrence while the third patient required reoperation for recurrent pyloric stenosis. No patient has suffered diarrhoea after vagotomy. Highly selective vagotomy is an effective treatment for urgent management of complicated duodenal ulceration and is without troublesome post-vagotomy symptoms.

(Med J Aust 1990; 152: 574-576)

In the last decade highly selective vagotomy has largely replaced truncal vagotomy and drainage [1-3] as the operation of choice for intractable chronic duodenal ulceration, mainly because it is associated with a very low mortality rate and has minimal postoperative sequelae.[4-8] However, in patients with complicated duodenal ulceration, highly selective vagotomy has been less uniformly employed. Johnston has obtained good early results using highly selective vagotomy for bleeding duodenal ulcer and pyloric stenosis,[9,10] as has Jordan for patients with perforated duodenal ulceration.[11]

In spite of the good results reported in the elective situation, highly selective vagotomy in the treatment of complicated duodenal ulceration has not been widely reported. It has been shown to be a successful procedure in the elective management of intractable duodenal ulceration at our hospital.[6] Encouraged by these results our unit has adopted a policy of using highly selective vagotomy in the management of patients with complicated duodenal ulcer. This paper reports the results of these procedures.

Patients and methods

Fifty-four patients underwent highly selective vagotomy as part of their procedure for the management of complicated duodenal ulceration between 1979 and 1985. A further patient underwent highly selective vagotomy and dilatation in 1974 and the result of this patient is included in the study. Review of patients was completed in December 1985.

Bleeding duodenal ulcer

Since 1979, it has been the policy of the gastric surgical unit that all patients undergoing operation for bleeding duodenal ulcer only underwent highly selective vagotomy and suture of the bleeding point. Criteria for operation were age over 60 years, being in shock on admission to hospital, a maximum transfusion threshold of four units of blood and recurrent or continued bleeding during hospital stay. Additionally, other illnesses and poor medical condition were indications for more expeditious surgery, and a policy of early operation was followed. During this period almost all ulcer surgery was performed by the unit.

Patient details, indication for surgery, associated illnesses and postoperative complications were recorded prospectively. A preoperative illness rating was calculated from the records. Each organ system which was diseased, as well as the presence of preoperative shock, was allocated one point and the total number was considered the "illness score" of that patient. Similarly, a morbidity score was derived by allocating each complication, such as pneumonia, stroke, acute myocardial infarction, one point and the sum of these being the morbidity score.

Stenotic duodenal ulcer

All patients undergoing operation for pyloric or duodenal stenosis underwent highly selective vagotomy unless there was associated gastric ulceration.

Department of Surgery, Repatriation General Hospital Concord, Hospital Road, Concord, NSW 2139.
Gregory L Falk, FRACS, Clinical Superintendent in Surgery.
John W Hollinshead, MD, FRACS, FACS, Staff Specialist Surgeon.
David J Gillett, MS, FRACS, FRCS, FACS, Consultant in Surgery and Head of Department.
Reprints: Mr G L Falk, 2nd Floor Clinic, Department of Surgery, Concord Hospital.

Perforated duodenal ulcer

A small selected group of fit patients with a history of chronic ulcer and minimal general peritoneal contamination underwent highly selective vagotomy with patch closure of the duodenum.

Review

All patients were reviewed after surgery by one of the three authors. Each patient was assigned a Visick grading using the method modified by Goligher et al.[4] Patients with symptoms suggestive of recurrent ulceration were submitted for endoscopy.

Results

A total of 55 patients underwent highly selective vagotomy for complicated duodenal ulceration. Major complications after the operation occurred in 13 patients (23%) and five patients died (9%). Minor complications occurred in a further 41% of patients, mostly respiratory and urinary. All deaths occurred in those patients with bleeding duodenal ulceration.

Review of 48 patients was completed at a mean period of 28 months (range, 4-132 months). Two patients were lost to review. Satisfactory results were obtained in 45 patients and three were considered symptomatic failures. Two of these patients had proven ulcer recurrence and the third had recurrent pyloric stenosis. The overall proven ulcer recurrence rate was 4%, and all recurrences occurred in the group of patients with pyloric stenosis.

Highly selective vagotomy in the treatment of bleeding duodenal ulcer

Thirty-three patients (three women, 30 men) with a mean age of 64 years underwent highly selective vagotomy and oversewing of the bleeding point. The mortality within this group was 15% (five patients). The patients have been grouped according to the presentation to the surgical service and mortality noted: group A — 25 patients admitted with bleeding duodenal ulcer (one death); group B — eight patients admitted with another illness who developed a bleeding duodenal ulcer during the hospital admission (four deaths).

The age, coincident illness and outcome of patients in these groups are listed below.

Characteristics	*Group A*	*Group B*
Number	25	8
Mean age (years)	61.8	71.2
Mean preoperative illness score	1.8	1
Number of deaths	1	4*

*$P<0.01$, Fisher's exact test.

One patient (4%) in group A died, an 85-year-old woman who aspirated during endoscopy before surgery. Group-B patients, by contrast, were older, had multiorgan disease and had a significantly higher mortality (Fisher's exact test, $P<0.01$). Two patients (6%) rebled within the perioperative period after highly selective vagotomy, one in each group. One patient died after reoperation for perioperative rebleeding. Three patients died from multiorgan failure. A further patient died suddenly of pulmonary embolism eight days after

TABLE: Outcome (Visick score) of highly selective vagotomy

Complication	No. of patients reviewed	Visick score 1	2	4
Bleeding ulcer	33*	23	3	—
Pyloric stenosis	16	10	3	3
Perforation	6	6	—	—

*Twenty-six patients were reviewed.

surgery, the convalescence having been uneventful to that point.

Twenty-six patients were reviewed at a mean period of 23 months after operation. Five patients had died perioperatively, and two were lost to follow-up. All 26 patients reviewed had satisfactory results, 23 patients being graded Visick score 1 and three graded Visick score 2 (Table). There was no late recurrent ulceration in this group.

Highly selective vagotomy in the treatment of duodenal ulcer causing stenosis

Sixteen patients underwent highly selective vagotomy and an ancillary procedure for duodenal ulcer causing stenosis. Finger dilatation was performed in 13 patients and was technically successful in 11. In two patients pyloric rupture occurred due to forceful dilatation. Both ruptures were primarily sutured and a gastroenterostomy performed. One patient was judged unsuitable for dilatation because of severe stricturing and required gastroenterostomy. Two patients underwent duodenoplasty for postbulbar stenosis. There was no mortality and only minor morbidity in this group. There was no perioperative complication subsequent to pyloric rupture.

All 16 patients were reviewed at a mean period of 34 months and 13 showed satisfactory results. Three patients did not have a satisfactory outcome (Table). One patient suffered stomal ulceration and dumping after intraoperative pyloric rupture and gastroenterostomy. Two other patients had recurrent stenosis. One patient was found to have a recurrent ulcer while the second patient developed stenosis subsequent to duodenoplasty and no ulcer recurrence was demonstrated. The proven ulcer recurrence rate for highly selective vagotomy in the stenotic group was 12% (2 in 16 cases).

Highly selective vagotomy for perforated duodenal ulcer

Highly selective vagotomy has been performed after the closure of perforation of six selected cases of perforated duodenal ulcer. All patients had chronic ulcer diathesis and one a recurrent perforation. One patient required concurrent gastroenterostomy as the duodenum had severe stenosis. There was no mortality and only minor morbidity. At review all patients were graded Visick score 1. There was no ulcer recurrence in this group.

Discussion

There have been numerous operations used to control duodenal ulcer diathesis — partial gastrectomy, varieties of vagotomy and drainage, and highly selective vagotomy. The mortality rate associated with each procedure is different being 1% to 2% for partial gastrectomy,[2,12,13] 0.9% for truncal vagotomy and drainage[1-3,14,15] and less than 0.2% for highly selective vagotomy. The postoperative morbidity of partial gastrectomy is well recognized.[12,13,16,17] Truncal vagotomy and drainage also has a high incidence of sequelae, in some series approaching 25%, most commonly caused by diarrhoea and dumping.[1,14,15,17,18] The aim of our practice has been to avoid the sequelae of truncal vagotomy and drainage by utilizing highly selective vagotomy in elective and now, complicated, duodenal ulcer disease.

Pimpl et al. have demonstrated that the mortality of surgery for bleeding ulcers is strongly correlated with preoperative status.[19] In our group-A patients treated with highly selective vagotomy and oversewing of the bleeding point there was a low mortality (4%), in spite of the majority having two coincident illnesses and an average age of 62 years.

Group-B patients fared considerably worse, 50% dying in the postoperative period. Pimpl et al. have demonstrated the rapidly rising mortality with age over 60 years and coincident illness.[19] Wara et al. report a 38% mortality in a similar group[20] and Thorne and Nyhus a 44% mortality in their series treated by gastrectomy.[21] The danger of bleeding complicating another illness has been demonstrated by Larson et al., with mortality increasing in their series from 19% to 30% if bleeding started in hospital.[22] These data demonstrate the effect of age and coincident illness on the mortality from

upper gastrointestinal haemorrhage.[23-27] This mortality rate is not acceptable and avenues other than operation should be evaluated in an attempt to improve these results. Selected patients in this high-risk group may benefit from endoscopic therapy as a preoperative stabilizing manoeuvre.[19,20,28,29]

The choice of operation also affects survival. In the 1960s it became evident that the mortality of massive gastrointestinal haemorrhage was reduced from 23%–36% for partial gastrectomy[21,26] to 6%–16% when truncal vagotomy and drainage was performed.[21,23,26,30] We have obtained results with highly selective vagotomy which are comparable with other series utilizing truncal vagotomy. Highly selective vagotomy and oversewing successfully controlled bleeding in our series, the 6% rebleeding rate being similar to that achieved with truncal vagotomy and drainage.[23,25,30]

Excellent symptomatic results were obtained on short-term review, all patients having a satisfactory outcome. These data support the proposal that highly selective vagotomy, in the emergency treatment of bleeding duodenal ulceration, is associated with a mortality and rebleeding rate which is comparable with that of truncal vagotomy and drainage, and is without the undesirable side effects of diarrhoea and dumping.

The standard management of pyloric or duodenal stenosis secondary to duodenal ulceration has been truncal vagotomy and drainage, or a resectional procedure with the attendant problems of diarrhoea and dumping.[1,14,15,17,18] Highly selective vagotomy and dilatation of the stenosis was initially proposed by Johnston et al. in 1973.[31]

Application of dilatation to all cases caused pyloric rupture in two of our patients and has been observed by others in 12% to 24% of cases (David Johnston, personal communication).[9,31,33] Rupture caused no complications in our series as it was recognized and immediate repair performed. Mortality with unrecognized posterior rupture has been reported.[31,33] We have subsequently adopted a selective approach, dilating only softer strictures to avoid this problem. Johnston also currently favours this selective approach to the treatment of pyloric stenosis (personal communication). Two of the three poor results in our series occurred in patients with severe stenosis.

We currently perform duodenoplasty for postbulbar stenosis and gastroenterostomy for high-grade pyloric stenosis. The choice of gastroenterostomy over pyloroplasty allows the potential for the gastroenterostomy to be reversed if dumping ensues, and also avoids a suture line in fibrotic tissue decreasing the possibility of anastomotic leakage.

Many authors have reported a high recurrence rate and poor control of symptoms after simple closure of perforated duodenal ulceration with up to 80% of patients developing recurrent symptoms and ulceration.[34-37] Christiansen et al. reported a randomized trial of simple closure compared with highly selective vagotomy and closure.[38] The ulcer recurred in 52% of the control group and only 26% had good symptomatic results. By contrast, 77% of the treatment group had a good outcome and ulcer recurrence was 16%. Others have performed highly selective vagotomy and closure with excellent results.[11,39,40] Our experience of this is limited but all six patients were graded Visick score 1 on review. Highly selective vagotomy does not appear to increase the perioperative morbidity of simple closure and markedly improves the long-term outcome.

The majority of patients with complications of duodenal ulceration can be successfully treated by highly selective vagotomy. The choice of highly selective vagotomy over truncal vagotomy and drainage all but abolishes symptoms after surgery in these patients. Highly selective vagotomy in the treatment of bleeding ulcer is suitable for the majority of patients and does not contribute to mortality, which appears related to the age and premorbid condition of the patient. Mortality in patients bleeding from a duodenal ulcer during a hospital admission for another illness is high and avenues other than surgery need evaluation.

References

1. Stoddard CJ, Johnson AG, Duthie HL. The four to eight year results of the Sheffield trial of elective duodenal ulcer surgery — highly selective or truncal vagotomy? *Br J Surg* 1984; 71: 779-782.
2. Stabile BE, Passaro E Jr. Duodenal ulcer: a disease in evolution. *Curr Probl Surg* 1984; 21: 1-79.
3. Hoffmann J, Jensen HE, Schulze S, et al. Prospective controlled vagotomy trial for duodenal ulcer — results after five years. *Br J Surg* 1984; 71: 582-585.
4. Goligher JC, Hill GL, Kenny TE, Nutter E. Proximal gastric vagotomy without drainage for duodenal ulcer: results after 5-8 years. *Br J Surg* 1978; 65: 145-151.
5. Amdrup E. Vagotomy 1983. *Int Surg* 1983; 68: 293-294.
6. Hollinshead JW, Smith RC, Gillett DJ. Parietal cell vagotomy: experience with 114 patients with prepyloric or duodenal ulcer. *World J Surg* 1982; 6: 596-602.
7. Amdrup E, Anderson D, Hostrup H. The Aarhus County vagotomy trial: I. An interim report on primary results and incidence of sequelae following parietal cell vagotomy and selective gastric vagotomy in 748 patients. *World J Surg* 1978; 2: 85-90.
8. Johnston D. Operative mortality and postoperative morbidity of highly selective vagotomy. *Br Med J* 1975; 4: 545-547.
9. McMahon MJ, Greenall MJ, Johnston D, Goligher JC. Highly selective vagotomy plus dilatation of stenosis compared with truncal vagotomy and drainage in the treatment of pyloric stenosis secondary to duodenal ulceration. *Gut* 1976; 17: 471-476.
10. Johnston D. Division and repair of the spincteric mechanism at the gastric outlet in emergency operations for bleeding peptic ulcer. A new technique for use in combination with suture ligation of the bleeding point and highly selective vagotomy. *Ann Surg* 1977; 186: 723-729.
11. Jordan PH. Proximal gastric vagotomy without drainage for treatment of perforated duodenal ulcer. *Gastroenterology* 1982; 83: 179-183.
12. Gillett DJ, Pheils MT. The surgical treatment of pyloric obstruction due to peptic ulceration. *Aust NJ J Surg* 1969; 38: 252-255.
13. Pulvertaft CN. The results of partial gastrectomy for peptic ulcer. *Lancet* 1952; 1: 225-231.
14. Goligher JC, Pulvertaft CN, DeDombal FT, et al. Clinical comparison of vagotomy and pyloroplasty with other forms of elective surgery for duodenal ulcer. *Br Med J* 1968; 2: 787-789.
15. Kennedy T, Connell AM, Love AHG, et al. Selective or truncal vagotomy? Five year results of a double blind, randomised, controlled trial. *Br J Surg* 1973; 60: 944-948.
16. Goligher JC, Riley TR. Incidence and mechanism of the early dumping syndrome after gastrectomy. A clinical and radiological study. *Lancet* 1952; 1: 630-636.
17. Goligher JC, Pulvertaft CN, DeDombal FT, et al. Five to eight-year results of Leeds York controlled trial of elective surgery for duodenal ulcer. *Br Med J* 1968; 2: 781-787.
18. Goligher JC, Pulvertaft CN, Irwin TT, et al. Five to eight-year results of truncal vagotomy and pyloroplasty for duodenal ulcer. *Br Med J* 1972; 1: 7-13.
19. Pimpl W, Boeckl O, Waclawiczeki HW, Heinerman M. Estimation of the mortality rate of patients with severe gastroduodenal haemorrhage with the aid of a new scoring system. *Endoscopy* 1987; 19: 101-106.
20. Wara P, Berg V, Amdrup E. Factors influencing mortality in patients with bleeding ulcer: review of 7 years' experience preceding therapeutic endoscopy. *Acta Chir Scand* 1983; 149: 775-785.
21. Thorne FL, Nyhus LM. Treatment of massive upper gastrointestinal haemorrhage: a ten year review. *Am Surg* 1965; 31: 413-419.
22. Larson G, Schmidt T, Gott J, et al. Upper gastrointestinal bleeding: predictors of outcome. *Surgery* 1986; 100: 765-773.
23. Hunt PS. Bleeding ulcer: timing and technique in surgical management. *Aust NZ J Surg* 1986; 56: 25-30.
24. Kim B, Hastings KW, Bordan D, et al. Risks of surgery for upper gastrointestinal haemorrhage: 1972 versus 1982. *Am J Surg* 1985; 149: 474-476.
25. Farris JM, Smith GK. Appraisal of the long-term results of vagotomy and pyloroplasty in 100 patients with bleeding duodenal ulcer. *Ann Surg* 1967; 166: 630-639.
26. Foster JH, Hunt TK, Dunphy JE. Emergency operation for massive upper gastrointestinal haemorrhage. *Br J Surg* 1964; 51: 757-758.
27. Hunt PS. Gastrointestinal haemorrhage. Edinburgh: Churchill Livingstone, 1986: 43.
28. Flescher D. The Washington Symposium on endoscopic laser therapy — April 1985. *Gastrointest Endosc* 1985; 31: 397-400.
29. Johnson JH, Sones JQ, Long BW, Posey EL. Comparison of heater probe and YAG laser in endoscopic treatment of major bleeding from peptic ulcers. *Gastrointest Endosc* 1985; 31: 175-180.
30. Snyder EN, Stellar CA. Results of emergency surgery for massively bleeding duodenal ulcer. *Am J Surg* 1968; 116: 170-176.
31. Johnston D, Lyndon PJ, Smith RB. Humphrey CS. Highly selective vagotomy without a drainage procedure in the treatment of haemorrhage, perforation and pyloric stenosis due to peptic ulcer. *Br J Surg* 1973; 60: 790-797.
32. Dunn DC, Thomas WEG, Hunter JO. Highly selective vagotomy and pyloric dilatation for duodenal ulcer with stenosis. *Br J Surg* 1981; 68: 194-196.
33. Rossie RL, Braasch JW, Cady B, Segwick CE. Parietal cell vagotomy for intractable and obstructing duodenal ulcer. *Am J Surg* 1981; 141: 482-486.
34. Wagenseen SL, Wray RL, Golden GT. Perforated duodenal ulcer. *Am J Surg* 1972; 123: 538-542.
35. Donaldson GA, Jarrett F. Perforated gastroduodenal ulcer disease at the Massachusetts General Hospital from 1952 to 1970. *Am J Surg* 1970; 120: 306-311.
36. Greco RS, Chow CE. Alternatives in the management of acute perforated duodenal ulcer. *Am J Surg* 1974; 127: 109-114.
37. Gray JG, Roberts AK. Definitive emergency treatment of perforated duodenal ulcer. *Surg Gynaecol Obstet* 1976; 143: 890-894.
38. Christiansen J, Andersen OB, Bonnesen T, Baekgaard N. Perforated duodenal ulcer managed by simple closure versus closure and proximal gastric vagotomy. *Br J Surg* 1987; 74: 286-287.
39. Wara P, Kristenson ES, Sorensen FH, et al. The value of parietal cell vagotomy compared to simple closure in a selected approach to perforated duodenal ulcer. Operative morbidity and recurrence rate. *Acta Chir Scand* 1983; 149: 585-589.
40. Sawyers JL, Herrington JL. Perforated duodenal ulcer managed by proximal gastric vagotomy and suture plication. *Ann Surg* 1977; 185: 656-659.

(Received June 7, 1989; accepted January 12, 1990).

DEVELOPMENTAL MINIMALLY INVASIVE SURGERY

Surgical management underwent a major revolution in the early 1990s with the rapid establishment of laparoscopy for many simple procedures in general surgery. This followed the development of adequate video technology to enable coordinated operating between the surgeon and the assistant and visualisation of the gastrointestinal cavity on a TV screen. Visualisation and technology became so good that the visual appreciation of anatomical structures rapidly approached or even exceeded that of open surgical laparotomy. Surgeons found themselves able to perform simple excisional procedures of the gallbladder and the appendix but more complicated procedures such as removal of stones from the common bile duct or complex restorative procedures such as fundoplication, anastomosis, and repair of abdominal wall hernia were a different matter. These more complex procedures required suitably advanced skills and at that stage, techniques had not yet developed. This meant patients could not benefit from the rapid recovery, decreased discomfort and early discharge from hospital if disease was more complex.

During this period I was able to perform and teach developmental procedures to enable more complex laparoscopic surgery which led to multiple publications of much more complex laparoscopy. This enabled major surgical procedures to be done with minimal morbidity, less pain, and a greatly shortened hospital stay. Multiple publications on the development of various more advanced laparoscopic procedures ensued, and the institution of the Sydney Advanced Laparoscopic Training (SALT) facility at Concord Hospital was undertaken to teach these skills. I held workshops teaching the skills required for more advanced laparoscopy between 2003 and 2007 for multiple surgeons from around Australia three to four times a year.

Laparoscopic Antireflux Surgery: One of the greater achievements of my career was the development of laparoscopic antireflux surgery, performing the first such procedure in Australia and publishing techniques and outcome around the same time as Bernard Dallemange (who is

credited with the first procedure done this way in the world), reported his initial procedures in France. The research focus of hiatal surgery and antireflux surgery was followed through my entire career and has been a large component of publication. This topic was repeatedly addressed and presented frequently by invitation, in international world congresses of oesophageal diseases as the techniques and results evolved.

General advances in complex laparoscopy: I introduced techniques for removal of stones from the common bile duct, and techniques for the most complex splenectomy. I contributed frequently to the literature , and spoke at many national meetings, on multiple aspects of more advanced laparoscopy. I performed the first laparoscopic large bowel resection for carcinoma in Australia in 1993. Techniques such as adrenalectomy, bowel resection and anastomosis, suturing techniques, laparoscopic stapling techniques, control of major blood vessels and fundoplication were taught in animal models during the SALT course weeks. I was invited to speak at national meetings on laparoscopic techniques for oesophagectomy in the early 1990s.

The publications in this section demonstrate the advancing edge of surgical technique in laparoscopy both nationally and internationally. Multiple presentations and posters at international meetings were undertaken. This led to my hospital unit of surgery being sought out by international surgeons for training every year for the last several decades. My colleague Estifanos Debru currently a senior surgeon in Calgary Canada, published an outstanding article of our techniques, with the lowest rate of common bile duct injury in the laparoscopic era due to the methods developed by our group, contributing substantially to the application of appropriate techniques to minimise the feared problem of bile duct injury during surgery. This article has been highly cited. I was instrumental very early in development of techniques for operative cholangiography which advanced surgeons' ability to manage stones outside the gallbladder leading to development of methods of removal of stones from the common bile duct by laparoscopy. This has now become an established technique partly due to my early publication

and teaching it repeatedly during the SALT causes. Publications in the French surgical literature increased exposure of the techniques. Following our report on duodenal perforation after ERCP, the technique of management espoused in this has become a standard of care nationally. Further techniques of complex oesophagogastric minimally invasive (laparoscopic)surgery were described for various different disease processes.

References:

1. Falk GL, D'Netto TJ, Little SC. Endoscopic atlas of fundoplication. European Surgery. 2020;52(1):48-52.

2. Falk GL, D'Netto TJ, Phillips S, Little SC. Pneumothorax: Laparoscopic Intraoperative Management During Fundoplication Facilitates Management of Cardiopulmonary Instability and Surgical Exposure. Journal of Laparoendoscopic & Advanced Surgical Techniques. 2018;28(11):1371-

3. Falk GL, Van der Wall H, Burton L, Falk MG, O'Donnell H, Vivian SJ. Fundoplication for laryngopharyngeal reflux despite preoperative dysphagia. Ann R Coll Surg Engl. 2017;99(3):224-7.

4. Dale GJ, Phillips S, Falk GL. The analgesic efficacy of intravenous lidocaine infusion after laparoscopic fundoplication: a prospective, randomized, double-blind, placebo-controlled trial. Local Reg Anesth. 2016;9:87-93.

5. Wyten R, Kelty CJ, Falk GL. Laparoscopic duodenojejunostomy for the treatment of superior mesenteric artery (SMA) Syndrome: case series. J Laparoendosc Adv Surg Tech A. 2010;20(2):173-6 6

6. Debru E, Dawson A, Leibman S, Richardson M, Glen L, Hollinshead J, et al. Does routine intraoperative cholangiography prevent bile duct transection? Surg Endosc. 2005;19(4):589-93.

7. Dally E, Falk GL. Teflon pledget reinforced fundoplication causes symptomatic gastric and esophageal lumenal penetration. Am J Surg. 2004;187(2):226-9.

8. Baladas HG, Borody TJ, Smith GS, Dempsey MB, Richardson MA, Falk GL. Laparoscopic excision of a Brunner's gland hamartoma of the duodenum. Surg Endosc. 2002;16(11):1636.

9. Richardson M, Harrison, R.I., Falk, G.L. Early symptomatic results of laparoscopic Heller's Myotomy and fundoplication for Achalasia. Le Journal de Coelio-Chirurgie. 2000;33:80-3.

10. Neale ML, Falk GL. In vitro assessment of back pressure on ventriculoperitoneal shunt valves. Is laparoscopy safe? Surg Endosc. 1999;13(5):512-5.

11. Smith GS, Isaacson JR, Dempsey MB, Falk GL. Laparoscopic excision of esophageal leiomyoma through an anterior esophagotomy. Dis Esophagus. 2001;14(3-4):278-9.

12. Falk GL, Harrison RI. Laparoscopic cut Collis gastroplasty: a novel technique. Dis Esophagus. 1998;11(4):260-2.

13. Harrison RI, Falk, G.L. A preliminary experience of laparoscopic choledochotomy with primary closure. Technique and results in 11 patients. Le Journal de Coelio-Chirurgie. 1998;26:70-3.

14. Falk GL, Harrison, R.I., Adams, I.P., Brancatissano, R.P. Fundoplication by laparoscopy: the learning curve and technical modifciations. The European Journal of Coelio-Surgery. 1997;4.

15. Nicholson IA, Falk GL, Mulligan SC. Laparoscopically assisted massive splenectomy. A preliminary report of the technique of early hilar devascularization. Surg Endosc. 1998;12(1):73-5.

16. Munro W, Brancatisano R, Adams IP, Falk GL. Complications of laparoscopic fundoplication: the first 100 patients. Surg Laparosc Endosc. 1996;6(6):421-3.

17. Brancatisano R, Falk, G.L. Fundoplicature laparoscpique. A propos d'une expérience personnelle:88 cas. Le Journal de Coelio-Chirurgie. 1995;13:63-7.

18. Robinson G, Hollinshead J, Falk G, Moulton J. Technique and results of Laparoscopic Choledochotomy for the management of bile duct calculi. Australian and New Zealand Journal of Surgery. 1995;65(5):347-9.

19. Scarlett PY, Falk GL. The management of perforation of the duodenum following endoscopic sphincterotomy: a proposal for selective therapy. Aust N Z J Surg. 1994;64(12):843-6.

20. Falk GL, Brancatisano RP, Hollinshead J, Moulton J. Laparoscopic fundoplication: a preliminary report of the technique and postoperative care. Aust N Z J Surg. 1992;62(12):969-72.

21. Falk GL, D'Netto TJ, Phillips S, Little SC. Pneumothorax: Laparoscopic Intraoperative Management During Fundoplication Facilitates Management of Cardiopulmonary Instability and Surgical Exposure. Journal of Laparoendoscopic & Advanced Surgical Techniques. 2018;28(11):1371-

Eur Surg
https://doi.org/10.1007/s10353-019-00615-1

european surgery
ACA Acta Chirurgica Austriaca

Endoscopic atlas of fundoplication

Gregory L. Falk · Trevor J. D'Netto · Sophia C. Little

Received: 21 August 2019 / Accepted: 26 September 2019

Dear Editor,

Due to the high frequency of laparoscopic anti-reflux surgery, many medical gastroenterologists are seeing patients after surgery and performing endoscopy. There is a variable level of experience among medical endoscopists.

This letter aims to help the medical endoscopist understand the surgical structure of fundoplication as well as possible defects.

Introduction

The appearances of fundoplication are not necessarily familiar to many gastrointestinal medical practitioners investigating patients for oesophagogastric symptoms. This brief description has been formulated as an aid to management for non-surgical gastroenterology practitioners. Appearances of normal and abnormal cardio-oesophageal junctions and normal and various disrupted fundoplications are included.

Prof. G. L. Falk, MBBS, FRACS, FACS (✉) ·
S. C. Little, AVBS(Hons I)
Sydney Heartburn Clinic, Suite 29,
12–18 Tryon Road, Lindfield, Australia
sydney.heartburn@gmail.com

Prof. G. L. Falk, MBBS, FRACS, FACS
Upper Gastrointesitinal Surgery, Concord Repatriation Hospital, Concord, Australia

Sydney University, Sydney, Australia

Dr. T. J. D'Netto, MBBS(Hons)
Sydney Adventist Hospital, Wahroonga, Australia

Endoscopic images

Hiatus hernia Showing the crural impression which moves on breathing, with the stomach draped over each margin and entering the chest (Fig. 1).

Normal 360° fundoplication The fundoplication appears snug around the endoscope with no impression of the hiatus on the upper stomach with sulci either side of the fundoplication wrap, and there is no effacement of the folds in the stomach suggestive of the fundoplication being overtight (Fig. 2 and 3).

270° fundoplication Normal appearance of a well-formed partial fundoplication with no sulci formation and obviously sub-diaphragmatic. Commonly utilized with oesophageal dysmotility or achalasia (Fig. 3 and 4).

Conical fundoplication The fundoplication is sub-diaphragmatic and the sulci remain; however, the most inferior border of the fundoplication is loose around the endoscope and may be associated with less adequate control of reflux symptomatology. A cylindrical fundoplication is more likely to be effective in reflux control (Fig. 5).

Small para-oesophageal hiatus hernia recurrence with fundoplication A small dimple beside the impression of the crural pillar indicates a small berry-sized piece of stomach slipped alongside the oesophagus often occurring in the posterior lateral left margin of the repair. May cause local atypical epigastric discomfort and occasionally a sensation of dysphagia. Heartburn may or may not be present (Fig. 6).

Re-herniated fundoplication and cardio-oesophageal junction Impression of the hiatus on the upper

Published online: 04 November 2019

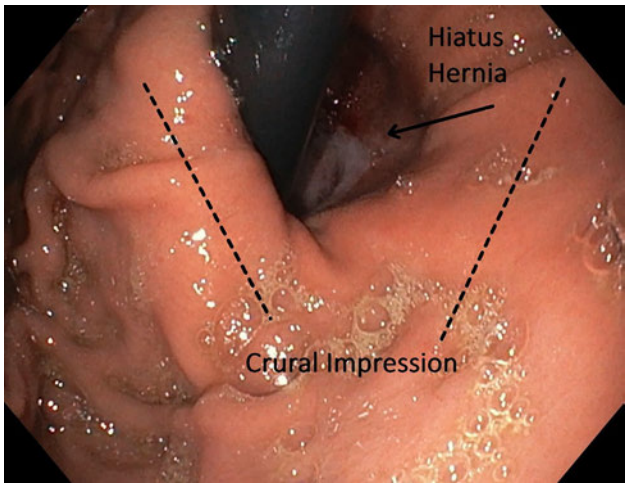


Fig. 1 Hiatus hernia

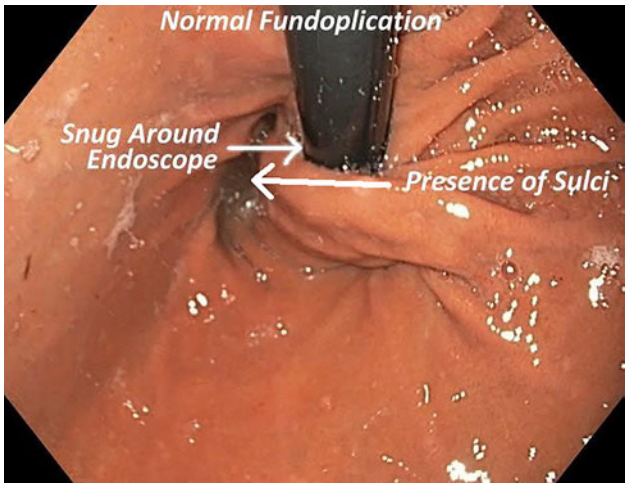


Fig. 2 Normal 360° fundoplication

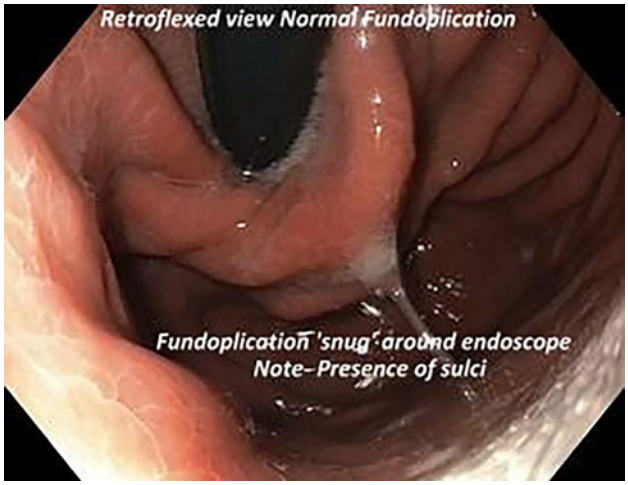


Fig. 3 Normal 360° fundoplication

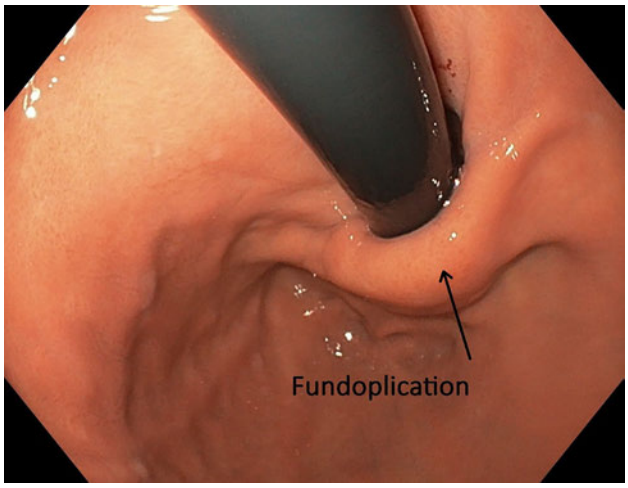


Fig. 4 270° fundoplication

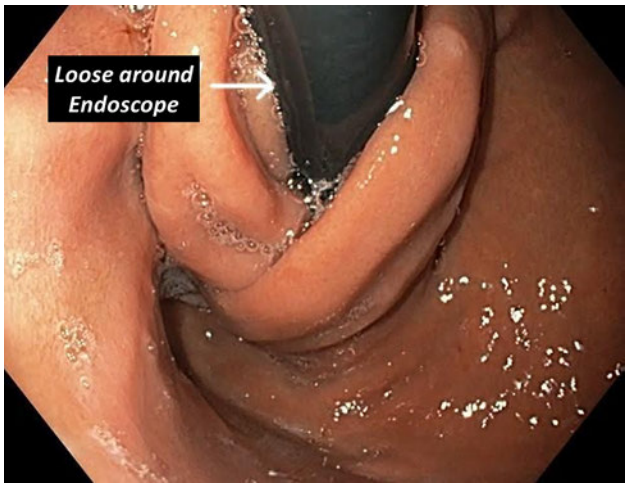


Fig. 5 Conical fundoplication

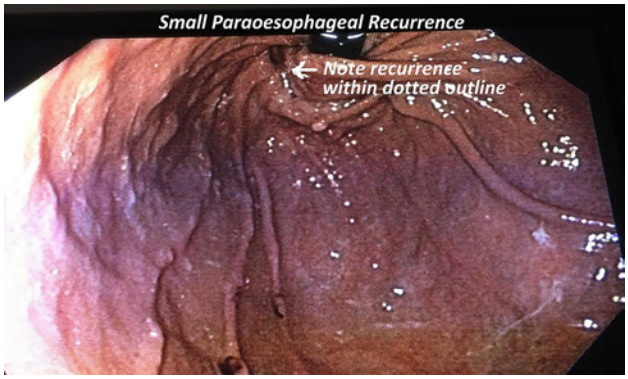


Fig. 6 Small para-oesophageal hiatus hernia recurrence with fundoplication

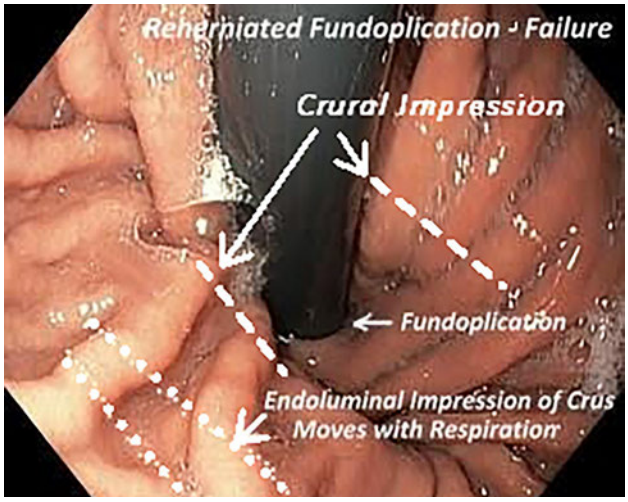


Fig. 7 Re-herniated fundoplication and cardio-oesophageal junction

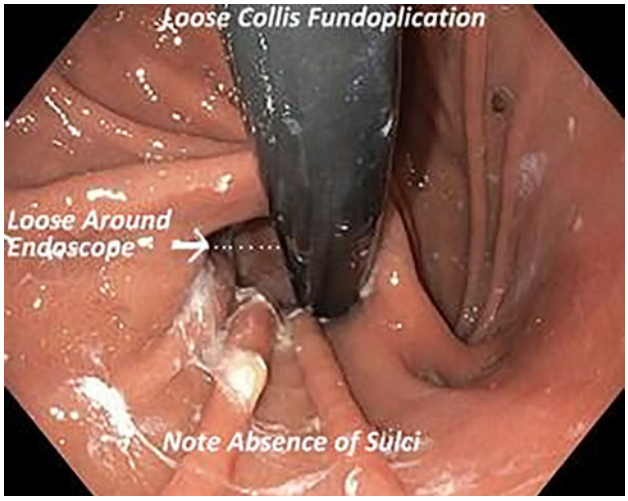


Fig. 8 Collis tube with fundoplication

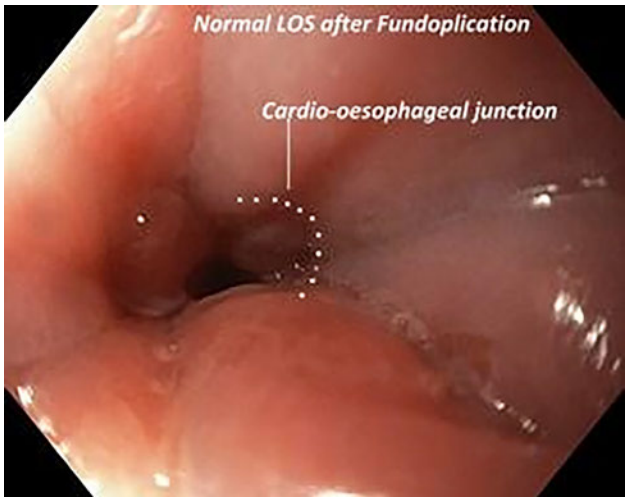


Fig. 9 Cardio-oesophageal junction with adequate fundoplication (viewed from oesophagus)

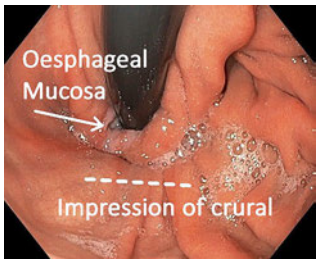


Fig. 10 Loose fundoplication

stomach marked by dotted lines. In real-time the respiratory movement may be seen with the fundoplication apparent around the endoscope and still intact but herniated. May be associated with poor control of reflux and dysphagia or may indeed be totally asymptomatic (Fig. 7).

Collis tube with fundoplication The Collis tube operation is where a short segment of oesophagus is lengthened with a staple line from the angle of His parallel to the lesser curve of the stomach for several centimetres and fundoplication is formed subdiaphragmatically around the tube of stomach. This procedure is usually performed for end-stage disease and is a compromise at best. In this case, the fundoplication is below the diaphragm but not adequately firm and lacks a 360° effect. Within the tube, one can see the gastric mucosa of the gastric tube. This is frequently mistaken for hiatus hernia. Prior to endoscopy, it is recommended that the operation report is obtained (Fig. 8).

Cardio-oesophageal junction with adequate fundoplication The proximal view of the cardio-oesophageal junction with modest opening upon air installation, no oesophagitis (Fig. 9).

Loose fundoplication The fundoplication has moved marginally upward and the impression of the crural pillar on the stomach may be seen. The fundoplication is not snug around the endoscope and the white squamous mucosa is just visualized. Likely to have recurrent heartburn and regurgitation (Fig. 10).

Discussion

Post-fundoplication gastroscopy is a useful tool in assessment of the anti-reflux mechanism. However, assessment of the mechanism by endoscopists is varied. The "Hill grades" of the retroflexed view of a fundoplication have been evaluated when measured against pH and oesophagitis [1]. These criteria have been estimated to be associated with worsening objective parameters of reflux disease following anti-reflux surgery. Grade one (Hill)—similar to on normal (Fig. 2). Grade two (Hill)—"valve slightly less well defined" (similar to Fig. 4). Grade three (Hill)—"ridge barely present, failure to close around the endoscope"

(similar to Fig. 10). Grade four (Hill)—no ridge apparent, hiatus hernia present (similar to Fig. 7).

Conclusion

Appreciation of these descriptions may enhance better evaluation by the physician endoscopist encountering post-operative patients.

Sincerely,
Prof Gregory L. Falk, Trevor J. D'Netto, and Sophia C. Little

Compliance with ethical guidelines

Conflict of interest G.L. Falk, T.J. D'Netto and S.C. Little declare that they have no competing interests.

Ethical standards Prospective patient data were collated from a password-protected practice database and collated for publication. The database was approved by the institutional ethics committee (CH62/6/2011-092).

References

1. Hill LD, Kozarek RA, Kraemer SJ, et al. The gastroesophageal flap valve: in vitro and in vivo observations. Gastrointest Endosc. 1996;44(5):541–7.

JOURNAL OF LAPAROENDOSCOPIC & ADVANCED SURGICAL TECHNIQUES
Volume 28, Number 11, 2018

DOI: 10.1089/lap.2018.0050

Pneumothorax: Laparoscopic Intraoperative Management During Fundoplication Facilitates Management of Cardiopulmonary Instability and Surgical Exposure

Gregory L. Falk, MB, BS, FRACS,[1,2] Trevor J. D'Netto, MB, BS (Hons),[1]
Stephanie Phillips, BMed, FRCA, FANZCA,[2] and Sophia C. Little, BAVBS (Hons)[1]

Abstract

Introduction: Intraoperative pneumothorax may complicate surgery by obscuring surgical view and cause cardiorespiratory instability during fundoplication with large hiatus hernia. Proactive intraoperative treatment may reduce conversion and drain insertion and facilitate timely completion of surgery.
Materials and Methods: The authors present effective surgical and anesthetic measures to alleviate pneumothorax, which are helpful for hemodynamic stability and surgical visibility.
Conclusion: Pneumothorax can complicate surgery by reducing surgical vision and causing cardiorespiratory instability. There is no requirement for laparoscopic or intercostal drainage. The authors provide various techniques to control intraoperative pneumothorax.

Keywords: fundoplication, hiatus hernia, pneumothorax, repair

Introduction

During fundoplication and other mediastinal surgery performed by laparoscopy, a pneumothorax (capnothorax) can potentially complicate surgery. It may cause both surgical and anesthetic intraoperative difficulties and perhaps compromise patient outcome, through cardiorespiratory instability and difficult surgical view. This is especially so in repair of large hiatus hernia.

Materials and Methods

Intraoperative pneumothorax has been treated in multiple different ways in a large single-surgeon practice of laparoscopic antireflux surgery. Pneumothorax appeared most frequently in treating very large hiatus hernia/paraesophageal hiatus hernia (PEH).[1]

Anesthetic management

The occurrence of pneumothorax in the elderly patient population with multiple comorbidities, in the head up position, may compromise cardiorespiratory function during anesthesia, causing sudden onset of hypotension, tachycardia, or bradycardia.[1] Such an occurrence frequently required returning the operating table to level and aspiration of carbon dioxide (CO_2) from the pleural space until the patient's hemodynamic situation stabilized. Pressors, atropine, and other agents were often necessary in a population group with a potential for cerebral ischemia. Management with intravenous arterial monitoring was valuable, allowing instantaneous detection of deteriorating blood pressure and facilitating early corrective intervention, which often appeared suddenly.

Surgical management

Identification and preservation of the pleura can prevent damage (Fig. 1); when the pneumothorax occurs, it is frequently visible as a rent in the pleura. The experienced surgeon will often instantaneously recognize a pleural breach and communicate this to anesthetics prior to the development of obvious pneumothorax and physiological deterioration (Fig. 2). Otherwise pneumothorax may appear as convex movement of the diaphragm or bulging on ventilation of the mediastinal pleura, frequently obscuring vision, and making

[1]Research Office, Sydney Heartburn Clinic, Lindfield, Australia.
[2]Department of Surgery, Sydney Adventist Hospital, Wahroonga, Australia.

dissection of the vagal nerves and posterior esophageal structures more difficult. Flattening the table and aspirating CO_2 are time consuming and temporary in nature, which requires further surgery performed at lower pressures with less adequate visualization. Avoidance of this situation is greatly advantageous in ease of surgery, potential for complications, and duration of surgery.

In our experience, as this condition occurred more commonly during surgery of PEH, however, dissection within the mediastinum emphasizing identification and preservation of the pleura decreased the incidence of inadvertent pneumothorax. Pleura was closely applied to the esophagus and often crossed the midline posteriorly. It was necessarily closely applied to the hernia sac and reduction of the hernia sac could pull the pleura into the operative field. Dissection of fatty tissue on the mediastinal surface of the sac and sweeping it back toward the lung helped preserve pleura. Absolute hemostasis aided vision of the pleura, for which harmonic scalpel was found highly useful (Johnston & Johnston Medical, Cincinnati, OH).

Multiple techniques were utilized to occlude pleural breach including PDS Endoloop (Fig. 3) (Ethicon Endo Surgery, Cincinnati, OH), a piece of hernia sack (Fig. 4), clips, hemostatic mesh gauze (Fig. 5), or V-lock suture (Covidien, Dublin,

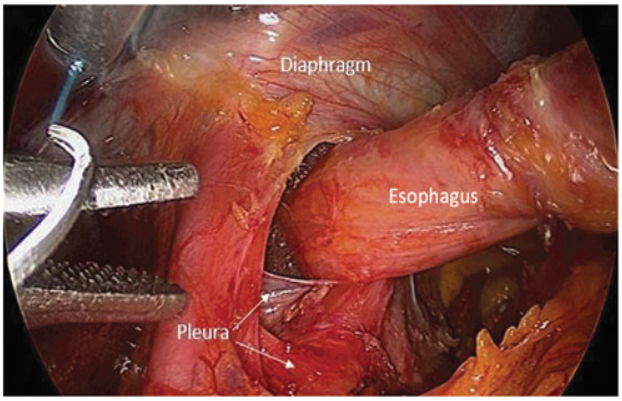


FIG. 1. Pleura: in the midline behind the esophagus.

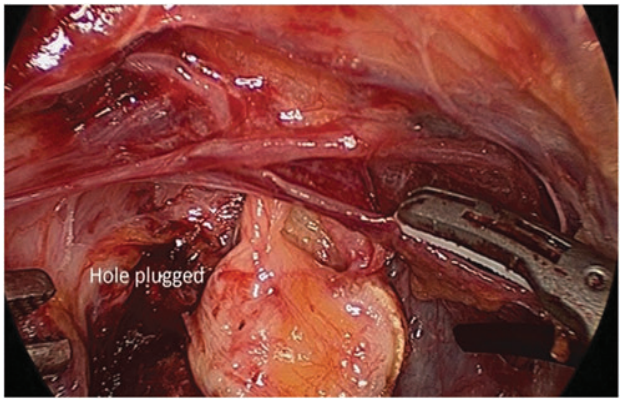


FIG. 4. Fat pad closure: small pleural defect ''plugged'' with sac material.

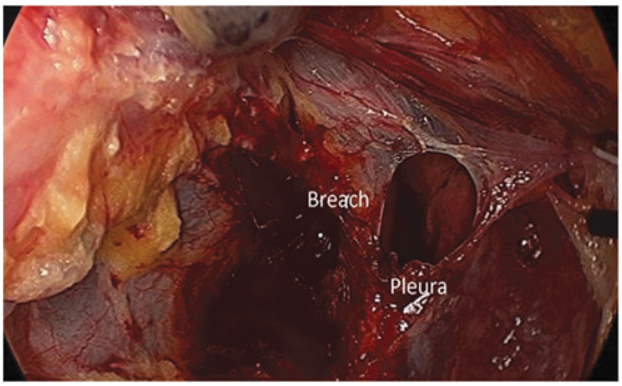


FIG. 2. Pneumothorax: circular breach in the pleura with lung in background.

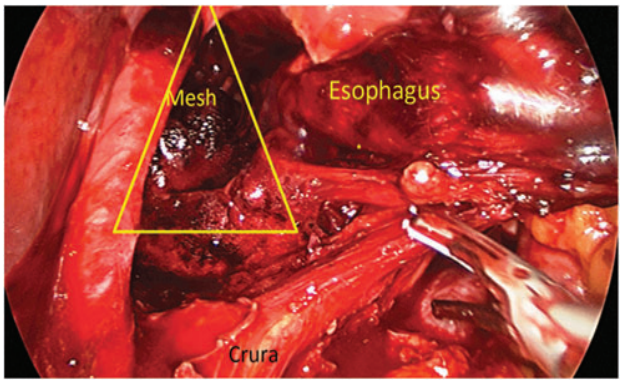


FIG. 5. Surgical mesh: wet mesh placed over a pleural breach.

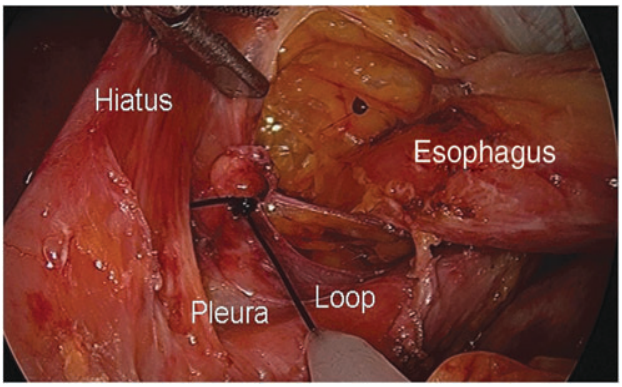


FIG. 3. Loop closure: PDS loop around breach in posterior right pleura.

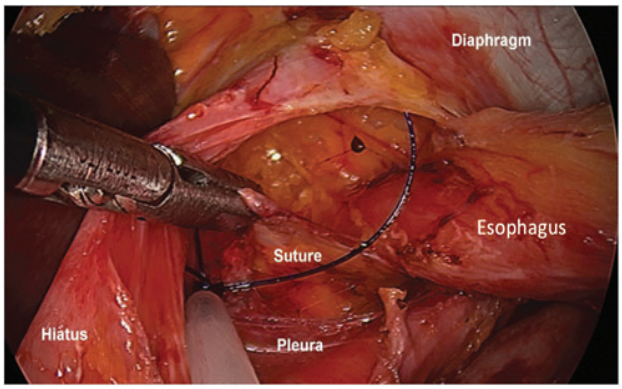


FIG. 6. V'lock suture: closure.

Ireland) (Fig. 6) for larger defects (Figs. 1–5). Occasionally two techniques may be combined.

The loop was utilized if a small hole could be easily grasped by the forceps and drawn into the loop. Alternatively, a large piece of hernial sac with minimal fat on it was ''pasted'' over the defect. Large amounts of fat in the mediastinum are avoided due to previous experience of fat necrosis causing a fibrotic esophageal stricture. Clips or a hemostatic sponge can work. Should one technique fail, an alternative can be sought. A large rent may be closed with barbed suture. Once closure is obtained, rapid lung reexpansion occurs as the CO_2 is reabsorbed.

Results of the Technique

All techniques were advantageous allowing better vision, stabilization of hemodynamic situation, and almost complete intraoperative resolution of the pneumothorax without necessity to decrease instillation pressure of CO_2. At completion of the case, a valsalva maneuver was performed with mediastinal suction and abdominal suction to remove the majority of the CO_2. Rapid resorption of small residual pleural gas amounts was then expected. Patients were returned to the recovery ward where chest X-ray was performed only if oxygen saturation was reduced after a period of 30 minutes of observation or there was respiratory or hemodynamic instability. No chest drains were required and no patient required open surgery after laparoscopic pneumothorax occurrence.

Conclusion

Although avoidance of pneumothorax is desirable and dissection with close attention to the pleural reflection advantageous, occasional breaches occur. Hemodynamic instability can be rapid. Early surgical treatment of this defect is desirable and adequate anesthetic monitoring necessary.

It has not been necessary to convert or pleurally drain any patient since this approach has been performed. Some authors[2–4] have recommended heroic management of intraoperative pneumothorax, including intercostal catheter and even thoracotomy. We have not found this to be necessary before intraoperative management and rapid seal of any defect has been technically easy and facilitates surgical exposure and timely completion of surgery.

Disclosure Statement

The authors declare no conflict of interest.

References

1. Phillips S, Falk GL. Surgical tension pneumothorax during laparoscopic repair of massive hiatus hernia: A different situation requiring different management. Anaesth Intensive Care 2011;39:1120–1123.
2. Joris JL, Chiche JD, Lamy ML. Pneumothorax during laparoscopic fundoplication: Diagnosis and treatment with positive end-expiratory pressure. Anesth Analg 1995;81: 993–1000.
3. Watson DI, Mitchell P, Game PA, et al. Pneumothorax during laparoscopic mobilization of the oesophagus. Aust N Z J Surg 1996;66:711–712.
4. Sternberg DM, Petrick AT, Gharagozloo F, et al. Tension pneumothorax precluding laparoscopic repair of a diaphragmatic hernia. Surg Laparosc Endosc 1997;7:429–431.

Address correspondence to:
Gregory L. Falk, MB, BS, FRACS
Sydney Heartburn Clinic
Suite 29, 12-18 Tryon Rd.
Lindfield, NSW 2070
Australia

E-mail: sydney.heartburn@gmail.com

Royal College of Surgeons
ADVANCING SURGICAL CARE

UPPER GI SURGERY

Ann R Coll Surg Engl 2017; **99:** 224–227
doi 10.1308/rcsann.2016.0330

Fundoplication for laryngopharyngeal reflux despite preoperative dysphagia

GL Falk[1], H Van der Wall[2], L Burton[2], MG Falk[1], H O'Donnell[1], SJ Vivian[1]

[1]Sydney Heartburn Clinic, Lindfield, Australia
[2]Concord Nuclear Imaging, Sydney, Australia

ABSTRACT

INTRODUCTION Fundoplication for laryngopharyngeal disease with oesophageal dysmotility has led to mixed outcomes. In the presence of preoperative dysphagia and oesophageal dysmotility, this procedure has engendered concern in certain regards.

METHODS This paper describes a consecutive series of laryngopharyngeal reflux (LPR) patients with a high frequency of dysmotility. Patients were selected for surgery with 24-hour dual channel pH monitoring, oesophageal manometry and standardised reflux scintigraphy.

RESULTS Following careful patient selection, 33 patients underwent fundoplication by laparoscopy. Surgery had high efficacy in symptom control and there was no adverse dysphagia.

CONCLUSIONS Evidence of proximal reflux can select a group of patients for good results of fundoplication for atypical symptoms.

KEYWORDS
Fundoplication – Laryngopharyngeal reflux – Cough – Reflux scintigraphy – Dysphagia

Accepted 11 October 2015

CORRESPONDENCE TO
Gregory Falk, E: sydney.heartburn@gmail.com

The 2006 Montreal consensus defined gastro-oesophageal reflux disease (GORD) as a condition that develops when reflux of stomach contents causes troublesome symptoms or complications.[1] Traditionally, patients have been identified with a range of extraoesophageal symptoms including cough, dysphonia, sore throat, atypical chest pain and pulmonary symptoms.[2] The non-specific nature of the symptoms has made diagnosis difficult. There is often no obvious heartburn or regurgitation.[3,4] The accuracy of test results have been brought into question as pH catheters (previously considered the gold standard) do not record poorly acidic or non-acid regurgitation and without dual channel catheters, the upper oesophagus remains diagnostically obscure.[5] The success rates for surgery for laryngopharyngeal reflux (LPR) (predominantly chronic reflux cough) have therefore stalled at 60–70% in most series.

No unequivocal test has been available to confirm that laryngeal and pulmonary symptoms are caused by the presence of gastro-oesophageal reflux. Diagnostic issues continue. Impedance reflux technology has enabled the measurement of non-acidic and mildly acidic reflux events.[6–8] However, even this does not adequately demonstrate reflux into the pharynx, with at least one study showing substantial intraobserver error.[9–11] Selection of patients for surgery has been troubled by diagnostic difficulty and surgical series consequently have relatively poor outcomes. Identification of non-acidic proximal reflux by impedance may help improve this.[12–14] Results can be influenced in a multifactorial fashion by the difficulty of diagnostic selection, surgical variability (especially in the occasional operator) and the many other illnesses with similar symptomatology. Fundoplication has always concerned surgeons in the presence of dysphagia and this group of patients frequently present with dysphagia among the symptoms.

Our report of a consecutive group of patients undergoing surgery for LPR predominant symptoms describes careful patient selection using reflux scintigraphy technology, 24-hour dual channel pH monitoring and an experienced multidisciplinary approach in a tertiary referral service. The uniquely evolved standardised scintigraphy is able to positively demonstrate pharyngeal or pulmonary contamination by reflux fluid.

Methods

The notes for a cohort of consecutive patients undergoing laparoscopic fundoplication during a four-year period for LPR predominant symptoms were extracted retrospectively from a prospectively populated database. The data were approved for reporting by the institutional ethics committee. Symptoms recorded were chronic cough (defined as existing for more than eight weeks' duration, with appropriate respiratory investigation),[15] dysphonia, throat clearing, sore throat, laryngospasm and clinical pulmonary aspiration as well as the typical GORD symptoms of heartburn dysphagia and regurgitation. Patients with continuing marked

symptoms despite a double dose of proton pump inhibitors (PPIs) were offered surgery. Reflux scintigraphy and pH monitoring with manometry were performed. Clinical reassessment was undertaken three months following surgery using a standardised proforma (Appendix 1 – available online).

pH monitoring

Monitoring of pH was performed over 24 hours using antimony crystal dual channel catheters (Synectics Medical Inc., Stockholm, Sweden). A standard technique was employed as described elsewhere.[11,12] The normal values for distal reflux were defined as pH >4, overall acid exposure <4% of total time and DeMeester composite score <14.7.[14] Any proximal reflux during the upright or supine period was considered abnormal.

Manometry

Stationery manometry was performed using a water perfused catheter (Dentsleeve, Mississauga, Ontario, Canada), as described elsewhere.[11,12] Oesophageal motility was graded for effectiveness using a system similar to that of Kahrilas *et al*[16] but using four quartiles rather than three groups.

Scintigraphy

A standardised scintigraphy technique described elsewhere[17,18] was employed, using technetium labelled pentetic acid in the initial erect and supine dynamic images. A delayed study was then obtained at two hours to evaluate the possibility of aspiration of refluxate into the lungs. Regions of interest were drawn over the pharynx and upper oesophagus, and time activity curves were generated for the erect and supine dynamic studies. These regions of interest were related back to the relevant background region of interest (Fig 1).

Fundoplication

Fundoplication was performed by laparoscopy and crural repair was carried out posteriorly in all cases. A technique similar to the Nissen–Rossetti procedure was employed for 360° fundoplication while partial fundoplication was by the Toupet or anterior 270° technique. The fundoplication was calibrated with a 52Fr bougie (female) and a 56Fr bougie (male). Non-absorbable sutures were employed and the fundoplication was approximated using anterior sutures 1cm apart to create a short, floppy fundoplication with division of a variable number of short gastric vessels to achieve adequate lack of tension on the fundoplication. The repair was fixed to the diaphragm laterally by 'crown' sutures. Toupet partial fundoplication was undertaken in the standard fashion, and anterior fundoplication was performed with multiple sutures of the stomach to the oesophagus and right crus.

Statistical analysis

Non-parametric statistical methods for ordinal data were employed. Analysis of variance, the Wilcoxon signed-rank test and the Pearson correlation coefficient (two-tailed) were used to compare the data. Statistical analysis was performed with STATISTICA version 8 (StatSoft, Tulsa, OK, US). A p-value of <0.05 was considered statistically significant for the clinical, pH and manometry data owing to a higher standard deviation than the scintigraphy data, for which statistical significance was set at $p<0.01$. Dysphagia and quality of life scores were evaluated with the paired t-test, comparing preoperative versus early postoperative and late postoperative scores.

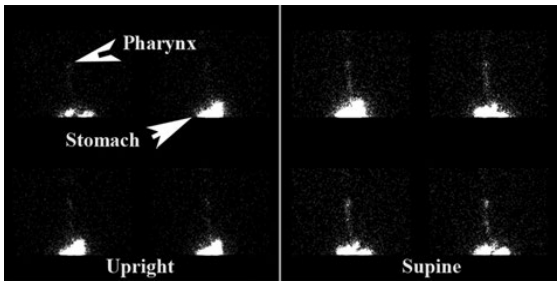


Figure 1 Scintigraphy showing pharyngeal contamination

Selection for surgery

Patients were selected with intractable symptoms persisting on a double dose of PPIs for more than six weeks, with confirmed proximal reflux on pH study and/or scintigraphy, pulmonary aspiration or full length oesophageal reflux to the pharynx. Other diagnoses were excluded routinely using a multidisciplinary approach comprising an ear, nose and throat specialist, a respiratory physician, a chest x-ray or chest computed tomography, diagnosis and treatment of asthma, and avoidance of medication likely to precipitate cough.

Results

Over the course of the 4 years studied, fundoplication was performed in 33 patients (20 female) with a mean age of 57 years (range: 38–72 years). LPR symptoms were reported in 32 patients, 1 patient having severe heartburn and sinusitis. LPR and GORD symptoms were reported in 22 of the 33 patients. Symptoms included cough (n=25), heartburn (n=24), regurgitation (n=23), voice change (n=15), throat clearing (n=11), pulmonary aspiration (n=11), sore throat (n=10), globus (n=5) and laryngospasm (n=2). The mean duration of symptoms was 4.8 years (range: 6 months – 22 years). Dysphagia was present in 24 patients (72%) preoperatively and severe in 15 patients (45%).

Surgical symptom control

Preoperative symptoms of LPR were eliminated in 27 patients (79%) following surgery and improved in a further 4, leading to a total good outcome for 31 patients (91%). Occasional chest pain and bloating was reported in four patients. There was reduction of cough in a further patient

from 15 episodes per day to 2 episodes. Another two patients showed resolution of cough after surgery while taking PPIs but reappearance occurred on stopping medication. There was no relief of LPR symptoms in one patient; however, postoperative scintigraphy showed no evidence of gastro-oesophageal reflux. Two patients were lost to follow-up.

Dysphagia

As well as preoperatively, dysphagia was assessed in the early (10 days) and late (3 months) postoperative period. Prior to surgery, dysphagia was present in 24 patients, with no dysphagia reported by the remaining 9. In the early postoperative period, worsened dysphagia was present in 5 patients, 16 had experienced no change and 4 experienced new onset of dysphagia. No dysphagia was reported by five patients and there were inadequate data for three patients. Late postoperative assessment found dysphagia improved in 19 patients, with 11 being free of dysphagia and inadequate data available for 3 patients. There was no difference between preoperative and early postoperative dysphagia ($p>0.05$) but late postoperative dysphagia was significantly improved (t=-4.2, 95% confidence interval: -6.4–-2.2, $p<0.05$). The mean preoperative and late postoperative scores for dysphagia and quality of life are shown in Table 1.

pH monitoring

The results of distal pH studies were abnormal in all patients. The mean number of episodes of reflux in the distal oesophagus was 128 and in the upper oesophagus, it was 31. The mean acid exposure time in the distal oesophagus was 16.4% when upright and 20.4% when supine. In the proximal oesophagus, it was 1.6% when upright and 10.5% when supine. In six patients, abnormal proximal reflux was present only when supine. Conversely, 16 patients had proximal reflux when upright but not when supine. The remaining 11 patients experienced proximal reflux in both positions.

Manometry

The mean oesophageal sphincter pressure was 2.9mmHg (standard deviation: 5.0mmHg; normal: >18mmHg). Ineffective oesophageal motility (IEM) was found in 24 patients; 16 were classified as having severe IEM. There was no correlation between IEM and preoperative, early postoperative or late postoperative dysphagia because of the high overall frequency of motility disturbance among the 33 patients.

Table 1 Comparison of mean quality of life and dysphagia scores before and after surgery

Indicator	Preoperative score (n=33)	Postoperative score at ~3 months (n=30)
GIQLI	90	102 (*higher score = improvement)*
Visick score	3	2 (*lower score = improvement)*
Dakkak dysphagia score	33	37 *(higher score = improvement)*

GIQLI = Gastrointestinal Quality of Life Index

Scintigraphy

Gastro-oesophageal reflux was noted in all patients on imaging. Pulmonary aspiration was identified in 17 patients (52%) in the delayed study obtained at 2 hours after initiation of the erect and supine dynamic studies. Pharyngeal contamination with isotope was observed in 27 patients (82%). There was increasing scintigraphic activity in the pharynx over time in nine patients and this was highly predictive of pulmonary aspiration ($p<0.01$). Presence of isotope in the pharynx correlated strongly with total percentage of proximal acid exposure time over the 24 hours of pH monitoring ($p<0.01$). Pulmonary aspiration on scintigraphy correlated strongly with total proximal acid exposure on pH monitoring ($p<0.01$).

Discussion

Subjecting patients with LPR symptoms to scintigraphy and pH monitoring allows the prediction of successful response to fundoplication. Successful response is suggested by: a) rising pharyngeal time-activity curves or presence of pulmonary aspiration on scintigraphy; and/or b) abnormal total proximal or supine proximal acid exposure time on pH studies. The degree to which symptoms were controlled was substantially higher than that reported in other studies.[19–29] Despite previous concerns regarding surgery, our study has shown improved results. This may be partly due to patient selection using standardised reflux scintigraphy and the severe nature of the reflux of the patients referred to a tertiary antireflux service. The group was highly selected and investigated intensively by multiple specialists.

Cough and LPR symptoms may be caused by direct exposure to noxious agents resulting in a decreased cough threshold,[30] local inflammation,[31] subcellular tight junction abnormalities, pulmonary aspiration or asthma-like symptoms. However, there is good evidence for a further mechanism, a neurally mediated cause of this symptomatology (reflex), which would not be detected by scintigraphy. This group of patients would therefore not be selected for surgery and it may be that many patients were denied effective surgery as a result. Strong correlation existed between positive results for proximal pH testing and pharyngeal and pulmonary soiling, indicating substantial laryngopharyngeal soiling.

Symptoms in the patient group in this study were caused by direct reflux damage rather than a neural reflex mechanism. The results obtained in this series are largely believed to be dependent on an experienced multidisciplinary approach to this condition in a dedicated antireflux surgical group. One cannot assume that such results would translate to a district hospital setting and general surgery. Patients with chronic cough in the community are likely to be an entirely different patient group and are therefore unlikely to benefit to the same extent.[11]

There was a high rate of preoperative and postoperative dysphagia, and most patients suffered severe IEM. Despite

the IEM, dysphagia improved significantly following surgery. The lower oesophageal sphincter was grossly deficient and reflected the selection of severe reflux patients.

Conclusions

Acceptable results for fundoplication in LPR patients can be obtained using a multidisciplinary approach including a standardised reflux scintigraphy technique, 24-hour dual channel pH monitoring and exclusion of alternative diagnoses. Dysphagia remains as a symptom preoperatively and postoperatively. There was a high rate of IEM in our patient group. This group was highly selected and one cannot therefore assume that our results are transferable to a community population with chronic cough.

References

1. Vakil N, van Zanten SV, Kahrilas P *et al.* The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; **101**: 1,900–1,920.
2. Koufman JA, Aviv JE, Casiano RR, Shaw GY. Laryngopharyngeal reflux: position statement of the Committee on Speech, Voice, and Swallowing Disorders of the American Academy of Otolaryngology – Head and Neck Surgery. *Otolaryngol Neck Surg* 2002; **127**: 32–35.
3. Dickman R, Kim J, Camargo L *et al.* Correlation of gastroesophageal reflux disease symptoms characteristics with long-segment Barrett's esophagus. *Dis Esophagus* 2006; **19**: 360–365.
4. Fass R, Dickman R. Clinical consequences of silent gastroesophageal reflux disease. *Curr Gastroenterol Rep* 2006; **8**: 195–201.
5. Gillison EW, Kusakari K, Bombeck CT, Nyhus LM. The importance of bile in reflux oesophagitis and the success in its prevention by surgical means. *Br J Surg* 1972; **59**: 794–798.
6. Vaezi MF. Laryngitis and gastroesophageal reflux disease: increasing prevalence or poor diagnostic tests? *Am J Gastroenterol* 2004; **99**: 786–788.
7. Sifrim D, Dupont L, Blondeau K *et al.* Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. *Gut* 2005; **54**: 449–454.
8. Tutuian R, Mainie I, Agrawal A *et al.* Nonacid reflux in patients with chronic cough on acid-suppressive therapy. *Chest* 2006; **130**: 386–391.
9. Faruqi S, Sedman P, Jackson W *et al.* Fundoplication in chronic intractable cough. *Cough* 2012; **8**: 3.
10. Zerbib F, Roman S, Bruley Des Varannes S *et al.* Normal values of pharyngeal and esophageal 24-hour pH impedance in individuals on and off therapy and interobserver reproducibility. *Clin Gastroenterol Hepatol* 2013; **11**: 366–372.
11. Smith JA, Houghton LA. The oesophagus and cough: laryngo-pharyngeal reflux, microaspiration and vagal reflexes. *Cough* 2013; **9**: 12.
12. Mainie I, Tutuian R, Agrawal A *et al.* Combined multichannel intraluminal impedance-pH monitoring to select patients with persistent gastro-oesophageal reflux for laparoscopic Nissen fundoplication. *Br J Surg* 2006; **93**: 1,483–1,487.
13. Aanen MC, Bredenoord AJ, Samsom M, Smout AJ. Reliability of oesophageal pH recording for the detection of gastro-oesophageal reflux. *Scand J Gastroenterol* 2008; **43**: 1,442–1,447.
14. Sifrim D, Blondeau K, Mantillla L. Utility of non-endoscopic investigations in the practical management of oesophageal disorders. *Best Pract Res Clin Gastroenterol* 2009; **23**: 369–386.
15. Janson C, Chinn S, Jarvis D, Burney P. Determinants of cough in young adults participating in the European Community Respiratory Health Survey. *Eur Respir J* 2001; **18**: 647–654.
16. Kahrilas PJ, Dodds WJ, Hogan WJ *et al.* Esophageal peristaltic dysfunction in peptic esophagitis. *Gastroenterology* 1986; **91**: 897–904.
17. Falk GL, Beattie J, Ing A *et al.* Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? *World J Gastroenterol* 2015; **21**: 3,619–3,627.
18. Falk M, Van der Wall H, Falk GL. Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms. *Nucl Med Commun* 2015; **36**: 625–630.
19. Ekström T, Johansson KE. Effects of anti-reflux surgery on chronic cough and asthma in patients with gastro-oesophageal reflux disease. *Respir Med* 2000; **94**: 1,166–1,170.
20. Farrell TM, Richardson WS, Trus TL *et al.* Response of atypical symptoms of gastro-oesophageal reflux to antireflux surgery. *Br J Surg* 2001; **88**: 1,649–1,652.
21. Greason KL, Miller DL, Deschamps C *et al.* Effects of antireflux procedures on respiratory symptoms. *Ann Thorac Surg* 2002; **73**: 381–385.
22. Novitsky YW, Zawacki JK, Irwin RS *et al.* Chronic cough due to gastroesophageal reflux disease: efficacy of antireflux surgery. *Surg Endosc* 2002; **16**: 567–571.
23. Thoman DS, Hui TT, Spyrou M, Phillips EH. Laparoscopic antireflux surgery and its effect on cough in patients with gastroesophageal reflux disease. *J Gastrointest Surg* 2002; **6**: 17–21.
24. Wright RC, Rhodes KP. Improvement of laryngopharyngeal reflux symptoms after laparoscopic Hill repair. *Am J Surg* 2003; **185**: 455–461.
25. Brouwer R, Kiroff GK. Improvement of respiratory symptoms following laparoscopic Nissen fundoplication. *ANZ J Surg* 2003; **73**: 189–193.
26. Duffy JP, Maggard M, Hiyama DT *et al.* Laparoscopic Nissen fundoplication improves quality of life in patients with atypical symptoms of gastroesophageal reflux. *Am Surg* 2003; **69**: 833–838.
27. Chang AB, Lasserson TJ, Kiljander TO *et al.* Systematic review and meta-analysis of randomised controlled trials of gastro-oesophageal reflux interventions for chronic cough associated with gastro-oesophageal reflux. *BMJ* 2006; **332**: 11–17.
28. Rakita S, Villadolid D, Thomas A *et al.* Laparoscopic Nissen fundoplication offers high patient satisfaction with relief of extraesophageal symptoms of gastroesophageal reflux disease. *Am Surg* 2006; **72**: 207–212.
29. Swoger J, Ponsky J, Hicks DM *et al.* Surgical fundoplication in laryngopharyngeal reflux unresponsive to aggressive acid suppression: a controlled study. *Clin Gastroenterol Hepatol* 2006; **4**: 433–441.
30. Qiu Z, Yu L, Xu S *et al.* Cough reflex sensitivity and airway inflammation in patients with chronic cough due to non-acid gastro-oesophageal reflux. *Respirology* 2011; **16**: 645–652.
31. Patterson RN, Johnston BB, Ardill JE *et al.* Increased tachykinin levels in induced sputum from asthmatic and cough patients with acid reflux. *Thorax* 2007; **62**: 491–495.

Appendix 1 Proforma for clinical reassessment at three months

Gastro-Intestinal Quality of Life Index

1. How often during the past 2 weeks have you had pain in the abdomen?
   ☐0 all of the time ☐1 most of the time
   ☐2 some of the time ☐3 a little of the time
   ☐4 never
2. How often during the past 2 weeks have you had a feeling of fullness in the upper abdomen?
   ☐0 all of the time ☐1 most of the time
   ☐2 some of the time ☐3 a little of the time
   ☐4 never
3. How often during the past 2 weeks have you had bloating (a sensation of too much gas in the abdomen)?
   ☐0 all of the time ☐1 most of the time
   ☐2 some of the time ☐3 a little of the time
   ☐4 never
4. How often during the past 2 weeks have you been troubled by excessive passage of gas through the anus?
   ☐0 all of the time ☐1 most of the time
   ☐2 some of the time ☐3 a little of the time
   ☐4 never
5. How often during the past 2 weeks have you been troubled by strong burping or belching?
   ☐0 all of the time ☐1 most of the time
   ☐2 some of the time ☐3 a little of the time
   ☐4 never
6. How often during the past 2 weeks have you been troubled by gurgling noises from the abdomen?
   ☐0 all of the time ☐1 most of the time
   ☐2 some of the time ☐3 a little of the time
   ☐4 never
7. How often during the past 2 weeks have you been troubled by frequent bowel movements?
   ☐0 all of the time ☐1 most of the time
   ☐2 some of the time ☐3 a little of the time
   ☐4 never
8. How often during the past 2 weeks have you found eating to be a pleasure?
   ☐4 all of the time ☐3 most of the time
   ☐2 some of the time ☐1 a little of the time
   ☐0 never
9. Because of your illness, to what extent have you restricted the kinds of food you eat?
   ☐0 all of the time ☐1 most of the time
   ☐2 some of the time ☐3 a little of the time
   ☐4 never
10. During the past 2 weeks, how well have you been able to cope with everyday stresses?
    ☐0 extremely poorly ☐1 poorly
    ☐2 moderately ☐3 well
    ☐4 extremely well
11. How often during the past 2 weeks have you been sad about being ill?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never
12. How often during the past 2 weeks have you been anxious about your illness?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never
13. How often during the past 2 weeks have you been happy with life in general?
    ☐4 all of the time ☐3 most of the time
    ☐2 some of the time ☐1 a little of the time
    ☐0 never
14. How often during the past 2 weeks have you been frustrated about your illness?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never
15. How often during the past 2 weeks have you been tired or fatigued?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never
16. How often during the past 2 weeks have you felt unwell?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never
17. Over the past week, have you woken up in the night?
    ☐0 every night ☐1 5–6 nights
    ☐2 3–4 nights ☐3 1–2 nights
    ☐4 never
18. Since becoming ill, have you been troubled by changes in your appearance?
    ☐0 a great deal ☐1 a moderate amount
    ☐2 somewhat ☐3 a little bit
    ☐4 not at all
19. Because of your illness, how much physical strength have you lost?
    ☐0 a great deal ☐1 a moderate amount
    ☐2 somewhat ☐3 a little bit
    ☐4 not at all
20. Because of your illness, to what extent have you lost your endurance?
    ☐0 a great deal ☐1 a moderate amount
    ☐2 somewhat ☐3 a little bit
    ☐4 not at all
21. Because of your illness, to what extent do you feel unfit?
    ☐0 extremely unfit ☐1 moderately unfit
    ☐2 somewhat unfit ☐3 a little unfit
    ☐4 fit

22. During the past 2 weeks, how often have you been able to complete your normal daily activities (school, work, household)?
    ☐4 all of the time ☐3 most of the time
    ☐2 some of the time ☐1 a little of the time
    ☐0 never
23. During the past 2 weeks, how often have you been able to take part in your usual patterns of leisure or recreational activities?
    ☐4 all of the time ☐3 most of the time
    ☐2 some of the time ☐1 a little of the time
    ☐0 never
24. During the past 2 weeks, how often have you been troubled by the medical treatment of your illness?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never
25. To what extent have your personal relations with people close to you (family or friends) worsened because of your illness?
    ☐0 very much ☐1 much
    ☐2 somewhat ☐3 a little
    ☐4 not at all
26. To what extent has your sexual life been impaired (harmed) because of your illness?
    ☐0 very much ☐1 much
    ☐2 somewhat ☐3 a little
    ☐4 not at all
27. How often during the past 2 weeks have you been troubled by fluid or food coming up into your mouth (regurgitation)?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never
28. How often during the past 2 weeks have you felt uncomfortable because of your slow speed of eating?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never
29. How often during the past 2 weeks have you had trouble swallowing your food?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never
30. How often during the past 2 weeks have you been troubled by urgent bowel movements?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never
31. How often during the past 2weeks have you been troubled by diarrhoea?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never
32. How often during the past two weeks have you been troubled by constipation?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never
33. How often during the past 2 weeks have you been troubled by nausea?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never
34. How often during the past 2 weeks have you been troubled by blood in the stool?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never
35. How often during the past 2 weeks have you been troubled by heartburn?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never
36. How often during the past 2 weeks have you been troubled by uncontrolled stools?
    ☐0 all of the time ☐1 most of the time
    ☐2 some of the time ☐3 a little of the time
    ☐4 never

Visik Score

37. What best describes the severity of your symptoms?
    ☐1 no symptoms
    ☐2 mild symptoms, simple care is effective
    ☐3 my symptoms interfere with my work or social life, simple care is ineffective
    ☐4 moderate or severe symptoms that interfere with my enjoyment of life, or recurring symptoms

Dysphagia Score

38. Do you have difficulty swallowing water?
    ☐0 always ☐2.5 sometimes ☐5 never
39. Do you have difficulty swallowing milk?
    ☐0 always ☐2.5 sometimes ☐5 never
40. Do you have difficulty swallowing custard?
    ☐0 always ☐2.5 sometimes ☐5 never
41. Do you have difficulty swallowing jelly?
    ☐0 always ☐2.5 sometimes ☐5 never
42. Do you have difficulty swallowing scrambled eggs?
    ☐0 always ☐2.5 sometimes ☐5 never
43. Do you have difficulty swallowing baked fish?
    ☐0 always ☐2.5 sometimes ☐5 never
44. Do you have difficulty swallowing bread?
    ☐0 always ☐2.5 sometimes ☐5 never
45. Do you have difficulty swallowing apple?
    ☐0 always ☐2.5 sometimes ☐5 never
46. Do you have difficulty swallowing steak?
    ☐0 always ☐2.5 sometimes ☐5 never

DeMeester Symptom Score

47. How often do you have reflux symptoms (heartburn, acid regurgitation, chest pain related to acidic foods or drinks)?
    ☐0 never
    ☐1 less than once a month

□2 more often that once a month but less than once a week
□3 more often than once a week but less than once a day
□4 daily

48. How long have you had these reflux symptoms?
□0 never □1 less than 6 mths
□2 6 mths – 2 years □3 2–5 years
□4 more than 5 years

49. How severe are these reflux symptoms?
□0 no symptoms
□1 mild symptoms
□2 spoil enjoyment of life
□3 interfere with life
□4 worst thing ever experienced

50. How satisfied are you with the results of your operation?
□0 I have had no operation
□1 not satisfied
□2 satisfied
□3 very satisfied

Laryngo-Pharyngeal Reflux Score

51. Within the last month, how did the following problems affect you?
(0 = no problem, 5 = all the time)
[A] Hoarseness or a problem with your voice
□ 0 □ 1 □ 2 □ 3 □ 4 □ 5
[B] Clearing your throat
□ 0 □ 1 □ 2 □ 3 □ 4 □ 5
[C] Excess throat mucous or postnasal drip
□ 0 □ 1 □ 2 □ 3 □ 4 □ 5
[D] Difficulty swallowing foods, liquids or pills
□ 0 □ 1 □ 2 □ 3 □ 4 □ 5
[E] Coughing after eating or lying down
□ 0 □ 1 □ 2 □ 3 □ 4 □ 5
[F] Breathing difficulties or choking episodes
□ 0 □ 1 □ 2 □ 3 □ 4 □ 5
[G] Troublesome or annoying cough
□ 0 □ 1 □ 2 □ 3 □ 4 □ 5
[H] Sensations of something sticking in your throat or a lump in your throat
□ 0 □ 1 □ 2 □ 3 □ 4 □ 5
[I] Heartburn, chest pain, indigestion or stomach acid coming up
□ 0 □ 1 □ 2 □ 3 □ 4 □ 5

Reflux edication

52. Are you using any acid/reflux medication?
□ Yes □ No
If yes, which medication and at what dose?

Reflux Symptom Sheet

Patient Name: _____

DOB _____

Appointment Date: _____

Predominant Category:

☐ LPR ☐ GOR ☐ MHH

Current Medications:

Predominant Symptom:

Symptoms

- ☐ Duration _____
- ☐ Heartburn _____ /10
- ☐ Regurgitation:
  - ☐ Low _____ /10
  - ☐ Throat _____ /10
- ☐ Odynophagia _____ /10
- ☐ Dysphagia:
  - ☐ Typical _____ /10
  - ☐ Slow transit _____ /10
- ☐ Vomiting _____ /10
- ☐ Nausea _____ /10
- ☐ Anorexia _____ /10
- ☐ Dyspepsia _____ /10
- ☐ Flatus _____ /10
- ☐ Bloat _____ /10
- ☐ Diarrhoea _____ /10
- ☐ Sleep disturbance:
  - ☐ Sit up to sleep _____ /10
- ☐ *Dyspnoea*
  - ☐ Exercise-induced _____ /10
  - ☐ Post-prandial _____ /10
  - ☐ Other _____ /10
- ☐ Atypical chest pain
  - ☐ Post-prandial _____ /10
  - ☐ Other _____ /10
- ☐ Palpitations _____ /10
- ☐ Early satiety _____ /10
- ☐ Tiredness/lethargy/pre-syncope _____ /10

Investigations

- ☐ Laryngoscopy _____
- ☐ CXR _____
- ☐ Smoking (Past) _____ (Present) _____
- ☐ PND _____
- ☐ High resolution CT
- ☐ RFTs
- ☐ Echo
- ☐ Gastroscopy
- ☐ Manometry
- ☐ 24hr pH
- ☐ Impedance

Symptoms

- ☐ Anaemia _____ /10
- ☐ Syncope _____ /10
- ☐ Cough _____ /10
- ☐ Cough duration _____
- ☐ Cough response to PPI? Y/N
- ☐ Globus _____ /10
- ☐ Mucous _____ /10
- ☐ Throat clearing _____ /10
- ☐ Sore throat _____ /10
- ☐ Dysphonia _____ /10
- ☐ Laryngospasm _____ /10
- ☐ Aspiration _____ /10
- ☐ Bronchitis (non-viral) _____ /10
- ☐ Pneumonia (non-viral) _____ /10
- ☐ Asthma:
  - ☐ Childhood _____ Suspected _____
  - ☐ Late onset _____ RFT proven _____
- ☐ Singing (history) _____ /10

Local and Regional Anesthesia

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

The analgesic efficacy of intravenous lidocaine infusion after laparoscopic fundoplication: a prospective, randomized, double-blind, placebo-controlled trial

Gregory J Dale[1]
Stephanie Phillips[2]
Gregory L Falk[3]

[1]Westmead Hospital Clinical School, The University of Sydney, [2]Sydney Adventist Hospital Clinical School, The University of Sydney, [3]Concord Clinical School, The University of Sydney, Sydney, Australia

Abstract: This study aimed to determine if intravenous lidocaine infusion reduces postoperative pain intensity following laparoscopic fundoplication surgery and to also validate the safety of intravenous lidocaine at the dose tested. This was an equally randomized, double-blind, placebo-controlled, parallel-group, single center trial. Adult patients undergoing laparoscopic fundoplication were recruited. The intervention group received 1 mg/kg intravenous lidocaine bolus prior to induction of anesthesia, then an intravenous infusion at 2 mg/kg/h for 24 hours. The primary outcome was pain, measured using a numeric rating scale for 30 hours postoperatively. Secondary outcomes were nausea and vomiting, opioid requirements, adverse events, serum lidocaine concentration, and length of hospital stay. The study was terminated after an interim analysis of 24 patients showed evidence of futility. There was no difference in postoperative pain scores (lidocaine versus control, mean ± standard deviation) at rest (2.0 ± 2.7 vs 2.1 ± 2.4, P=0.286) or with movement (2.0 ± 2.6 vs 2.6 ± 2.7, P=0.487). Three adverse events occurred in the lidocaine group (25% of patients). Intravenous lidocaine did not provide clinically significant analgesia to patients undergoing laparoscopic fundoplication. The serum lidocaine concentration of patients who experienced adverse events were within the therapeutic range. This trial cannot confirm the safety of intravenous lidocaine at the dose tested.

Keywords: analgesia, local anesthetics, intravenous infusions, pharmacokinetics

Introduction

Despite multimodal analgesia, severe postoperative pain is still experienced by many patients. Opioids are relatively contraindicated following laparoscopic fundoplication as they often cause nausea and vomiting. Postoperative vomiting places undue pressure on the repaired diaphragm and gastric wrap, risking early failure of the surgery.[1] As such, patients undergoing laparoscopic fundoplication need effective, parenteral, nonopioid analgesia.

Lidocaine is an inexpensive and widely accessible local anesthetic that possesses analgesic, anti-inflammatory, and antihyperalgesic properties.[2–4] While most commonly used in infiltration and for central neuraxial and peripheral nerve blocks, lidocaine can also be given intravenously (IV) to treat acute perioperative pain[4] and chronic neuropathic pain.[5] The current evidence for using IV lidocaine to treat perioperative pain is based on 45 clinical trials contributing to five systematic reviews.[4,6–9] These studies found that IV lidocaine infusion in the perioperative period decreases pain intensity, opioid requirements, the duration of postoperative ileus, and opioid-related

Correspondence: Gregory J Dale
Westmead Hospital, Cnr Hawkesbury Road and Darcy Road, Westmead, Sydney, NSW 2145, Australia
Email gregory.dale@health.nsw.gov.au

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/LRA.S119483

side-effects, such as postoperative nausea and vomiting. These studies concluded that further research is needed to determine the optimum dose, timing, and duration of infusion of lidocaine in this setting.

The effect of IV lidocaine infusion has not been studied in patients undergoing laparoscopic fundoplication surgery. This randomized controlled trial tested the primary hypothesis that IV lidocaine decreases postoperative pain intensity (at rest and during movement) after laparoscopic fundoplication. In order to verify the safety of IV lidocaine infusion for analgesia, the following secondary outcomes were measured: nausea and vomiting, opioid requirements, adverse events, serum lidocaine concentration, and length of hospital stay.

Methods

Study population

This was an equally randomized, double-blind, placebo-controlled, parallel-group, single-center trial conducted at the Sydney Adventist Hospital, Wahroonga, Sydney, Australia. Approval was received from the Adventist HealthCare Limited Human Research Ethics Committee (EC00141) and written informed consent was obtained from all patients. The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12613000440729).

All adults (age >18 years) undergoing laparoscopic fundoplication surgery by a single surgeon (GLF) were eligible to participate in the study. Exclusion criteria were allergies to local anesthetics, chronic use of analgesics or corticosteroids, impaired hepatic function (any single liver function test ≥20% normal reference range), epilepsy or other seizure disorder, severe cardiac failure (left ventricular ejection fraction ≤0.35) or cardiac arrhythmias and pregnancy.

Procedures

General anesthesia was standardized using midazolam 2.5 mg IV, effect-site target controlled infusions of propofol and remifentanil. Tracheal intubation was facilitated by rocuronium 1.2 mg/kg, and the lungs were ventilated with 33% oxygen in air using a circle system.

Intraoperatively, all patients received IV granisetron 3 mg and dexamethasone 8 mg as prophylaxis against nausea and vomiting and parecoxib 40 mg for analgesia. Postoperative analgesia was commenced with fentanyl 1 μg kg^{-1} IV at the cessation of the remifentanil infusion. The diaphragmatic crura and port sites were infiltrated with 20 mL ropivacaine 0.2% by the surgeon. A patient-controlled analgesia (PCA) device administering IV fentanyl was provided (10 μg/mL, 10 μg bolus, 5 minute lockout, no background) and PCA usage was recorded. Fentanyl PCA was discontinued if nausea was reported by the patient. Acetaminophen (1 g IV every 6 hours) and indomethacin (100 mg per rectum every 12 hours) were administered to provide multi-modal analgesia. Rescue antiemetics (ondansetron 4 mg sublingual and droperidol 0.5 mg/kg IV) were offered to any patient who experienced nausea or vomiting. Postoperatively, all patients had electrocardiogram monitoring via telemetry for 24 hours.

Patients were randomly assigned to study groups in fixed blocks of 12 using a computer-generated table of random numbers through the use of the randomization.com program. No stratification was used.

The patients in the intervention group received 1 mg/kg IV lidocaine bolus at induction, followed immediately by an infusion at 2 mg/kg/h for 24 hours. The patients in the control group were treated likewise using 0.9% sodium chloride in a double-blind fashion.

Lidocaine was acquired as Xylocard® 500 ampoules (AstraZeneca Pty Ltd, North Ryde, NSW, Australia), containing 500 mg of lidocaine hydrochloride in 5 mL of water. Lidocaine study drug was made to a concentration of 0.5% (5 mg/mL) and supplied in 1000 mL flasks compatible with IMED Gemini (IMED Corporation, San Diego, CA, USA) infusion pumps and giving sets. The lidocaine and placebo study drug were visually identical. No patient, research nurse, investigator, or any other medical or nursing staff was aware of the treatment assignments for the duration of the study.

The randomization schedule was stored in a locked cupboard that was only accessible by the randomization authority (thus concealed from all care providers and other research personnel). When a patient was recruited into the study, the randomization authority would prepare the appropriate study drug. The study drug was given to the anesthetist accompanied by a sealed, opaque, tamper-proof envelope containing the treatment allocation. This envelope was kept in the patient file at all times in case serious adverse event required the knowledge of treatment allocation. Envelopes were examined at the completion of the trial to ensure that they were unopened.

The primary outcome of the study was postoperative pain. Pain was assessed using an 11-point numeric rating scale (NRS-11). The patients were asked to score their current pain on two occasions: at rest and on mobilization from supine to sitting upright. Pain scores were obtained every 4 hours, for 30 hours following commencement of the trial drug infusion. The 11-point numeric rating scale is a validated, sensitive tool for assessing postoperative pain intensity.[10,11] All trial data were entered directly into the electronic medical record, which had been adapted for the study and mandated the completion of all parameters.

Secondary outcomes were nausea and vomiting, opioid requirements, adverse events, serum lidocaine concentration, and length of hospital stay. Patients were asked if they experienced any nausea or vomiting in the preceding 4 hours when pain scores were obtained. Responses were recorded as "yes" or "no" and this outcome was treated as binary data. Opioid requirements were recorded as the dose of fentanyl delivered (rather than total demands/attempts for analgesia). Only adverse events that required the patient to be discontinued from the trial were interpreted. Venous blood samples were collected from all patients every 4 hours for the duration of the trial. Serum was immediately separated and frozen, then later analyzed to determine the serum lidocaine concentration–time profile for the dosage regimen used in this study. Length of hospital stay was recorded as the number of nights the patient was in hospital.

Statistical analyses

A priori sample size was estimated on the basis of an absolute reduction in pain score. A reduction of two in the NRS-11 was reported to be the amount needed to cause a clinically significant reduction in a person's experience of postoperative pain.[12,13] A sample size of 18 patients in each group was calculated to be sufficient to detect a difference of two in the mean pain score, assuming a standard deviation of ±2[12] with a significance level α=0.05 and a power of 90%.

Interim analysis was planned when 33% and 66% of subjects had been recruited. The study would be stopped early when there was sufficient evidence to claim superiority (net benefit) or inferiority (net harm), or futility (little chance of achieving statistical significance) if the futility index was found to be >0.8.[14]

Statistical analyses were performed using IBM SPSS Statistics v21.0 (IBM Corporation). Sample size calculations and conditional power analyses were performed using PASS v13 (NCSS, LLC). The comparison between the intervention and control groups was conducted using an independent samples *t*-test, Mann–Whitney–Wilcoxon *U*-test, chi-squared test, or Fisher's exact test as appropriate. Normally distributed data are presented as mean ± standard deviation, nonnormally distributed data are presented as medians (interquartile range), and categorical data are presented as raw data and as frequencies. All statistical tests are two-sided with significance level α=0.05. Unblinding was performed prior to the statistical analysis of data.

Results

Twenty-four patients entered the study and were randomized equally to two groups. Twelve patients (100%) in the control group completed the study. Nine patients (75%) in the intervention group completed the study. The three patients who did not complete the study were withdrawn due to adverse events suspicious of lidocaine toxicity (treatment allocation was not known until after withdrawal from the trial). The participant flow diagram is presented (Figure 1). A planned interim analysis was performed when recruitment was 66% complete. At this point, the trial was stopped early on the basis of futility, prior to reaching the target sample size of 36 patients (18 per group). The futility index was 99%, that is, there was a 1% chance of rejecting a false null hypothesis at the end of the study given the data that had emerged.[15]

The demographic and clinical characteristics of both groups were similar (Table 1). There was no statistically significant difference in pain scores between treatment groups either at rest or during mobilization when summarized over the 30-hour postoperative period. At rest, the mean pain score was 2.0 ± 2.7 in the lidocaine group and 2.1 ± 2.4 in the control group (*P*=0.286). With movement, the mean pain score was 2.0 ± 2.6 in the lidocaine group and 2.6 ± 2.7 in the control group (*P*=0.487). Box and whisker plots are presented for pain scores at rest (Figure 2) and during mobilization (Figure 3) for lidocaine and control groups stratified at 6-hour intervals over the 30-hour postoperative period.

The incidence of nausea in the lidocaine group (50%) was similar to that in the control group (33%) (*P*=0.408). Three patients (25%) in the lidocaine group vomited, whereas one patient (8%) in the control group vomited (*P*=0.273).

The average total dose of fentanyl administered was 124 ± 165 μg for the lidocaine group and 344 ± 426 μg for the control group over the 30-hour postoperative period (*P*=0.117).

There were three clinically significant adverse events in the lidocaine group (25% of patients) compared with none in the control group, however, this difference was not statistically significant (*P*=0.064). One adverse event, severe bradycardia causing loss of consciousness, responded rapidly to external cardiac massage. The other adverse events were neurological symptoms (perioral paresthesia and restless legs) that are associated with early local anesthetic toxicity. The maximum serum lidocaine concentrations in these patients were 4.3, 2.7, and 3.5 mg/L.

The serum concentration–time profile of 12 patients who received the IV lidocaine infusion is presented in Figure 4. Two patients (22%) had peak serum lidocaine concentration ≥5 mg/L (5.2 and 5.0 mg/L). Neither of these patients experienced clinical signs or symptoms of lidocaine toxicity.

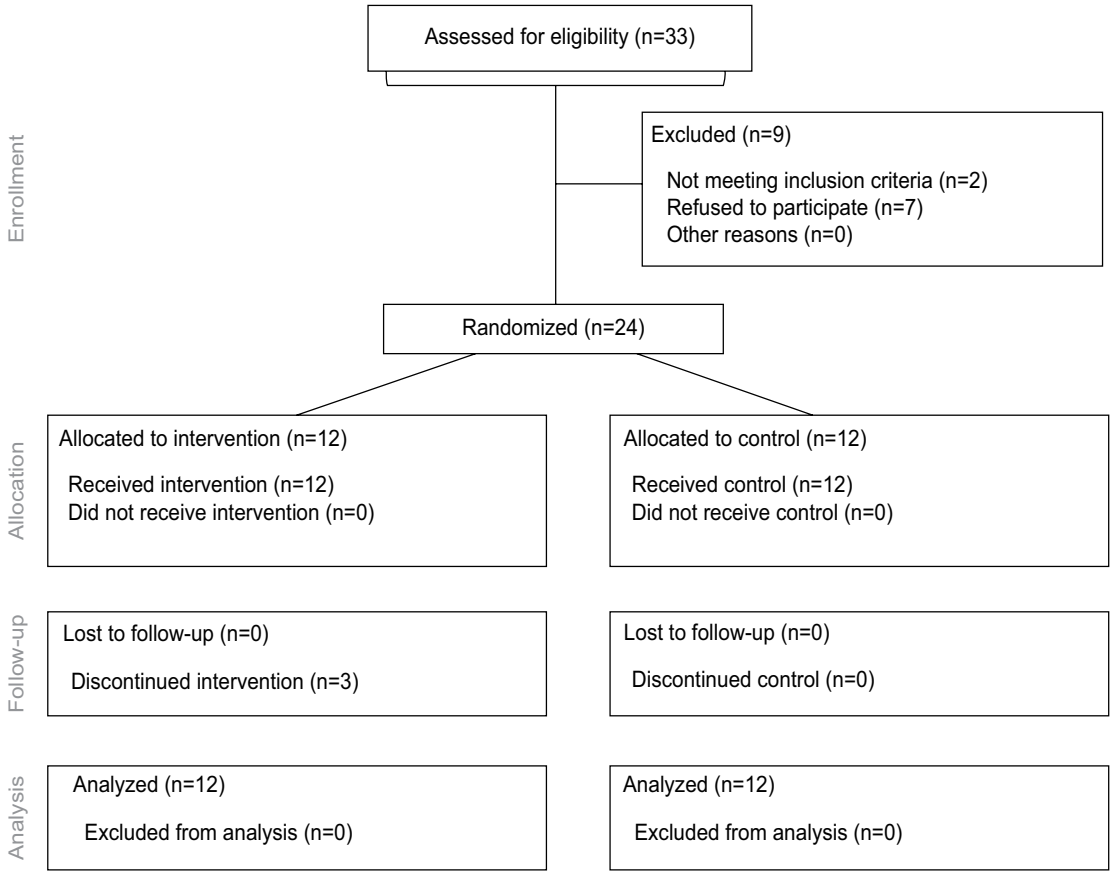


Figure 1 The CONSORT methods diagram showing participant flow.
Abbreviation: CONSORT, consolidated standards of reporting trials.

Table 1 Characteristics of patients undergoing laparoscopic fundoplication

	Lidocaine (n=12)	Control (n=12)
Age (years)	68.5 (10.17)	66.5 (11.39)
Sex (female)	9 (75%)	6 (50%)
Smoking status (current)	1 (8.33%)	1 (8.33%)
Height (cm)	165.75 (9.76)	165.33 (10.69)
Body mass index (kg/m^2)	27.05 (2.39)	28.91 (4.26)
Alcohol consumption (g/week)	77 (83.40)	68 (120.06)
ASA status*	2.33 (0.49)	2.27 (0.47)
Stomach herniated (%)	0.40 (0.28)	0.21 (0.27)
Surgery time (min)	68.83 (20.76)	64.50 (19.58)
Remifentanil used (μg/kg/h)	5.33 (2.16)	4.79 (1.70)
Propofol used (mg/kg/h)	0.445 (0.187)	0.461 (0.109)

Notes: *Physical status score. Values are mean (SD) or number (proportion).
Abbreviations: ASA, American Association of Anesthesiologists; SD, standard deviation.

There was no statistically significant difference in the mean length of hospital stay between groups; lidocaine group 2.5 days (95% confidence interval [CI] 2.07–2.93) and control group 2.25 days (95% CI 1.96–2.54).

Discussion

This study used a high dose and long duration of intravenous lidocaine infusion in an attempt to identify a concentration- or time-dependent analgesic effect. Despite this, a clinically significant benefit of lidocaine was not demonstrated. This study cannot reject the possibility that a small amount of analgesia is achieved with intravenous lidocaine. A mean reduction of 0.54 (95% CI: −1.56, 0.48) in pain score during mobilization was found in this study. This effect size is similar to that reported in the meta-analysis,[4] which showed intravenous lidocaine to reduce pain scores by 1.05 (95% CI: −1.68, −0.42) during activity at 6 hours after surgery and by 0.4 (95% CI: −0.8, −0.009) at 24 hours after surgery. This study was underpowered to detect such a small difference in pain scores between groups.

Intravenous lidocaine infusion has only shown benefit (in reducing pain, nausea, opioid consumption, bowel function, and reducing hospital stay) in patients following surgery of the bowel or gall bladder,[8] with the exception of radical prostatectomy.[16] The studies of intravenous lidocaine for patients undergoing abdominal hysterectomy,[17] orthopedic surgery,[18] tonsillectomy,[19] or coronary artery bypass[20] could not identify any benefits of lidocaine. Based on the available evidence, it appears that the analgesic efficacy of lidocaine is dependent on the surgical procedure performed. We propose that the analgesic efficacy of lidocaine relates to the afferent (sensory) innervation of the manipulated tissues and the type of nociceptive pain associated with this innervation.

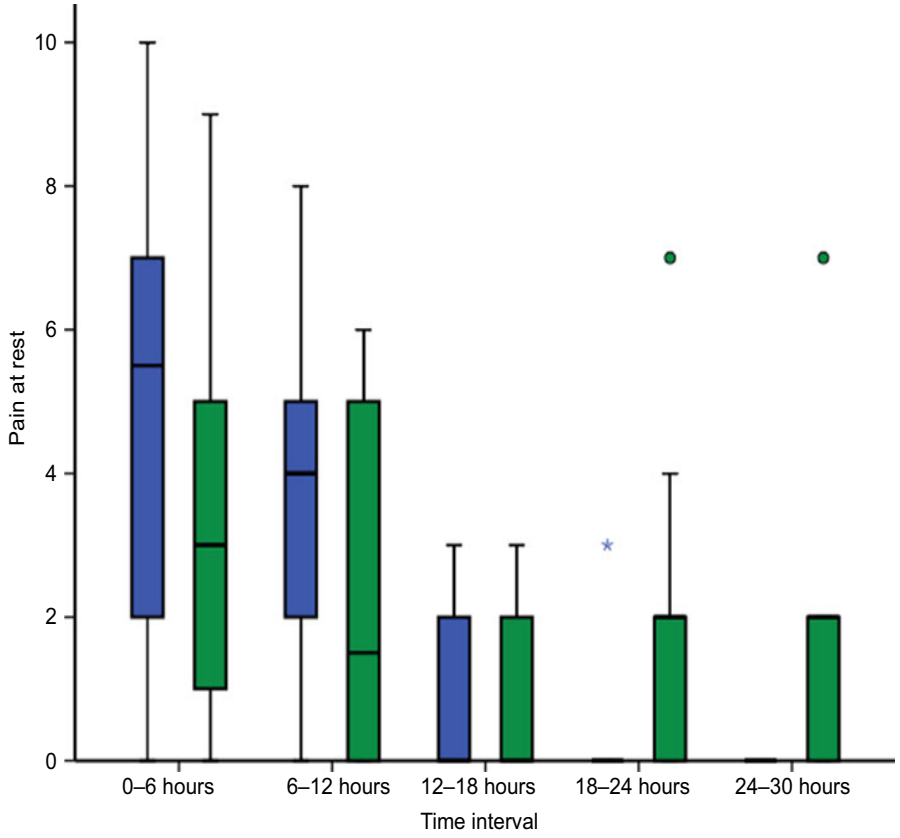


Figure 2 Box and whisker plot of pain scores at rest for lidocaine (blue) and control groups (green) at 6-hour intervals for 30 hours following laparoscopic fundoplication.
Notes: ○, outlier; ⋆, extreme outlier. Pain was assessed using an 11-point numeric rating scale (NRS-11). No significant difference between groups.

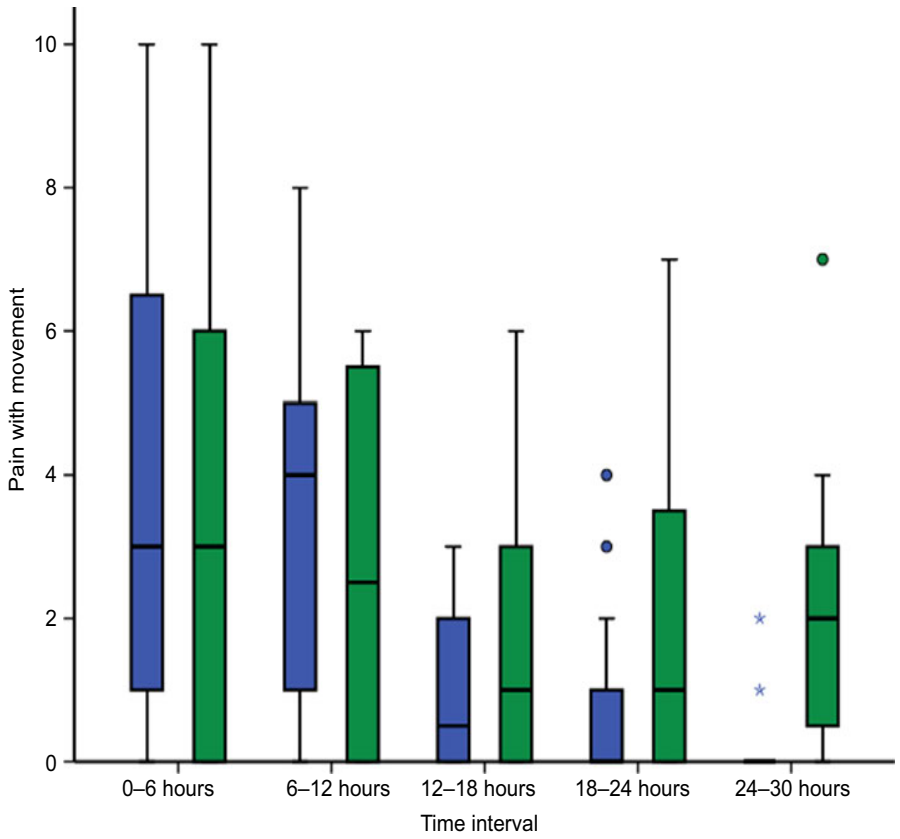


Figure 3 Box and whisker plot of pain scores with movement for lidocaine (blue) and control groups (green) at 6-hour intervals for 30 hours following laparoscopic fundoplication.
Notes: ○, outlier; ⋆, extreme outlier. Pain was assessed using an 11-point numeric rating scale (NRS-11). No significant difference between groups.

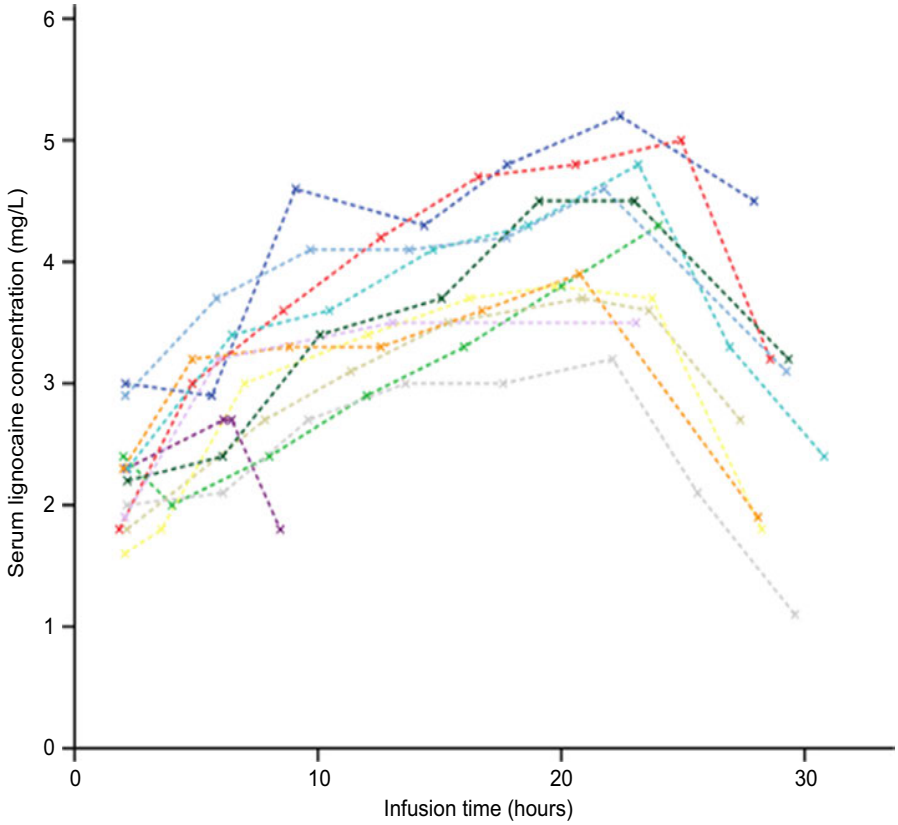


Figure 4 Serum concentration-time profile of lidocaine for each of the 12 patients receiving an intravenous lidocaine infusion (1 mg/kg loading dose, then 2 mg/kg/h for 24 hours).
Note: Different colored lines represent each of the 12 patients.

It would seem that intravenous lidocaine has the potential to improve postoperative analgesia following abdominal surgical procedures associated with visceral pain or postoperative ileus. Laparoscopic fundoplication predominantly involves surgical manipulation of the diaphragm, which receives somatic sensory innervation via the phrenic nerve. The pneumoperitoneum and tissue combustion plume that are associated with laparoscopic surgery may also irritate the parietal peritoneum. Since there seems to be a greater proportion of somatic pain than visceral pain associated with laparoscopic fundoplication, this may explain why an analgesic benefit of lidocaine was not observed in this study.

This study had a higher incidence of lidocaine toxicity than previous studies. No correlation was found between the occurrence of adverse events and serum lidocaine concentration, however, this is not unusual, as local anesthetic toxicity is described as being insidious and often unexpected.[21] Clinical signs and symptoms of lidocaine toxicity can occur below the much quoted "toxic threshold" of 5 mg/L, as there are inter-individual differences between lidocaine serum concentration and its therapeutic or toxic effects.[22] The greater number of adverse events seen in this study may be partially explained by the additional monitoring that the patients received. This unpredictability in safety may limit the clinical utility of intravenous lidocaine for postoperative analgesia.

The patients in this study were found to have greater serum lidocaine concentration at steady-state than was anticipated. The clearance of lidocaine in this study population was 7.9 ± 1.32 mL/kg/min, ~20% less than the estimate used when formulating the dosage regimen.[23] This study found that an infusion rate of 33 μg/kg/min (2 mg/kg/h) resulted in mean steady state serum concentration of 4.1 mg/L. An infusion rate of 26 μg/kg/min (1.6 mg/kg/h) would have been required to result in the intended steady state serum concentration of 3.3 mg/L in this population.

The weakness of this study is the small sample size because the trial was stopped early on the grounds of futility. We acknowledge that this trial has a higher risk of Type II error and it cannot exclude the possibility of a true effect size less than the minimum effect size of interest stipulated in the power calculation, however, we believe that it would have been an improper use of resources and unacceptable risk to patient safety in continuing the trial given the improbability of achieving statistical significance even if the entire a priori sample size was recruited. The strengths of this study are the validity of the randomized controlled trial methodology, the integrity of data collection, and close monitoring of patients for adverse events. As such, this well-designed, albeit small, study could contribute to future systematic reviews and meta-analyses in this field.

Further investigation is warranted to define the optimal dosage regimen for intravenous lidocaine to balance analgesic efficacy and patient safety. Only when an evidence-based dosage protocol has been derived should further studies be performed to identify which surgical procedures or patient populations may benefit from intravenous lidocaine.

This study does not support the use of intravenous lidocaine infusion for analgesia in patients undergoing laparoscopic fundoplication surgery. Intravenous lidocaine cannot be recommended for analgesia until a safe dosage regimen has been determined and the surgical procedures for which patients can benefit from intravenous lidocaine infusion have been identified.

Acknowledgments

The authors would like to acknowledge the staff at Sydney Adventist Hospital for their time and expertise that they dedicated to the project, Adventist HealthCare Limited for kindly facilitating the trial, and Sophie Liang for statistical support. Presented at the Australian Society of Anesthetists National Scientific Congress October 2014. This trial has not received sponsorship from the pharmaceutical industry.

Disclosure

GJD received research scholarships from the University of Sydney for his involvement in the project. The authors report no other conflicts of interest in this work.

References

1. Iqbal A, Kakarlapudi GV, Awad ZT, et al. Assessment of diaphragmatic stressors as risk factors for symptomatic failure of laparoscopic Nissen fundoplication. *J Gastrointest Surg*. 2006;10(1):12–21.
2. Taniguchi T, Shibata K, Yamamoto K, Mizukoshi Y, Kobayashi T. Effects of lidocaine administration on hemodynamics and cytokine responses to endotoxemia in rabbits. *Crit Care Med*. 2000;28(3):755–759.
3. Abram SE, Yaksh TL. Systemic lidocaine blocks nerve injury-induced hyperalgesia and nociceptor-driven spinal sensitization in the rat. *Anesthesiology*. 1994;80(2):383–391.
4. Sun Y, Li T, Wang N, Yun Y, Gan TJ. Perioperative systemic lidocaine for postoperative analgesia and recovery after abdominal surgery: a meta-analysis of randomized controlled trials. *Dis Colon Rectum*. 2012;55(11):1183–1194.
5. Mao J, Chen LL. Systemic lidocaine for neuropathic pain relief. *Pain*. 2000;87(1):7–17.
6. Marret E, Rolin M, Beaussier M, Bonnet F. Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. *Br J Surg*. 2008;95(11):1331–1338.
7. Vigneault L, Turgeon AF, Cote D, et al. Perioperative intravenous lidocaine infusion for postoperative pain control: a meta-analysis of randomized controlled trials. *Can J Anaesth*. 2011;58(1):22–37.
8. McCarthy GC, Megalla SA, Habib AS. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. *Drugs*. 2010;70(9):1149–1163.
9. Kranke P, Jokinen J, Pace NL, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. *Cochrane Database Syst Rev*. 2015;70(9):1149–1163.
10. Breivik EK, Björnsson GA, Skovlund E. A comparison of Pain Rating Scales by sampling from clinical trial data. *Clin J Pain*. 2000;16(1):22–28.
11. Hjermstad MJ, Fayers PM, Haugen DF, et al; European Palliative Care Research Collaborative (EPCRC). Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. *J Pain Symptom Manage*. 2011;41(6):1073–1093.
12. DeLoach LJ, Higgins MS, Caplan AB, et al. The visual analog scale in the immediate postoperative period: intrasubject variability and correlation with a numeric scale. *Anesth Analg*. 1998;86(1):102–106.
13. Farrar JT, Portenoy RK, Berlin JA, et al. Defining the clinically important difference in pain outcome measures. *Pain*. 2000;88(3):287–294.
14. Piantadosi S. *Clinical Trials: A Methodologic Perspective*. New York: John Wiley & Sons; 2005.
15. Proschan MA, Lan KG, Wittes JT. *Statistical Monitoring of Clinical Trials: A Unified Approach*. New York: Springer Science & Business Media; 2006.
16. Groudine SB, Fisher HA, Kaufman Jr RP, Patel MK, Wilkins LJ, Mehta SA, Lumb PD. Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain, and shortens hospital stay in patients undergoing radical retropubic prostatectomy. *Anesth Analg*. 1998;86(2):235–239.
17. Bryson GL, Charapov I, Krolczyk G, Taljaard M, Reid D. Intravenous lidocaine does not reduce length of hospital stay following abdominal hysterectomy. *Can J Anaesth*. 2010;57(8):759–766.
18. Martin F, Cherif K, Gentili ME, et al. Lack of impact of intravenous lidocaine on analgesia, functional recovery, and nociceptive pain threshold after total hip arthroplasty. *Anesthesiology*. 2008;109(1):118–123.
19. Striebel HW, Klettke U. Is intravenous lidocaine infusion suitable for postoperative pain management? *Schmerz*. 1992;6(4):245–250.
20. Insler SR, O'Connor M, Samonte AF, Bazaral MG. Lidocaine and the inhibition of postoperative pain in coronary artery bypass patients. *J Cardiothorac Vasc Anesth*. 1995;9(5):541–546.
21. Davison R, Parker M, Atkinson Jr AJ. Excessive serum lidocaine levels during maintenance infusions: Mechanisms and prevention. *Am Heart J*. 1982;104(2, Part 1):203–208.
22. Collinsworth KA, Kalman SM, Harrison DC. The clinical pharmacology of lidocaine as an antiarrhythymic drug. *Circulation*. 1974;50(6):1217–1230.
23. Burm A, Van Kleef J, Vermeulen N, Olthof G, Breimer DD, Spierdijk J. Pharmacokinetics of lidocaine and bupivacaine following subarachnoid administration in surgical patients: simultaneous investigation of absorption and disposition kinetics using stable isotopes. *Anesthesiology*. 1988;69(4):584–592.

JOURNAL OF LAPAROENDOSCOPIC & ADVANCED SURGICAL TECHNIQUES
Volume 20, Number 2, 2010

DOI: 10.1089/lap.2009.0237

Laparoscopic Duodenojejunostomy for the Treatment of Superior Mesenteric Artery (SMA) Syndrome: Case Series

Rebecca Wyten, BSc, MBBS, Clive J. Kelty, MBChB, PhD, FRCSEd, FRCS (Gen Surg), and Gregory L. Falk, MBBS, FRACS, FACS

Abstract

Superior mesenteric artery (SMA) syndrome is an atypical, rare cause of both acute and chronic high intestinal obstruction. Identification of this syndrome can be a diagnostic dilemma and is frequently made by exclusion. The most characteristic symptoms are postprandial epigastric pain, eructation, fullness, and voluminous vomiting. Symptoms are caused by compression of the third portion of the duodenum against the posterior structures by a narrow-angled SMA. When nonsurgical management is not possible or the problem is refractory, surgical intervention is necessary. In this article, we report a case series of SMA syndrome in 3 patients with radiologic evaluation confirming compression of the third portion of the duodenum by the SMA with resultant proximal dilatation. The patients all successfully underwent laparoscopic duodenojejunal anastomosis.

Introduction

Superior mesenteric artery (SMA) syndrome was described in 1861 by the Austrian physician and philosopher, Carl Freiherr von Rokitansky[1] and, since then, has been described by many researchers as rare and difficult to diagnose. SMA syndrome has been defined as a condition in which the third portion of the duodenum is compressed between the superior mesenteric neurovascular bundle anteriorly and the vertebral column posteriorly. This compression leads to either an acute or chronic presentation of intermittent emesis and postprandial abdominal pain. Many pathophysiologic factors to the syndrome lead to a mechanical obstruction of the third portion of the duodenum. Extensive investigations usually include an upper gastrointestinal contrast study, endoscopy, abdominal ultrasound (U/S), angiography, and multislice computer tomography (CT). Conservative medical management is advocated as the first line of treatment, but surgical management is considered in cases where this has failed. Previously, open duodenojejunostomy was considered the most successful surgical intervention, but recent advances in laparoscopic techniques have made laparoscopic duodenojejunostomy a safe, efficacious option.

Case Report 1

A 41-year-old female presented with an acute history of right-upper quadrant pain. Her associated symptoms included nausea, vomiting, and fever. Her past medical history included quadriplegia secondary to a C6–C7 cervical subluxation, cervical myelopathy, rheumatoid arthritis, psoriasis, and a cholecystectomy 7 weeks previously. On admission, her liver-function tests were deranged, suggestive of cholangitis, and the patient was treated with antibiotics. A plain abdominal X-ray showed a dilated stomach and associated dilatation of the 2nd (D2) and 3rd (D3) part of the duodenum with multiple air-fluid levels. The patient was treated conservatively with nasogastric tube decompression. U/S was unremarkable. After 5 days of conservative management, a CT scan displayed dilatation of the proximal duodenum and stomach, as well as nonspecific thickening of the sigmoid and descending colon with surrounding inflammation. Due to the dilatation of the proximal duodenum to D3, where it is interposed between the SMA and the aorta, a diagnosis of SMA syndrome was made. Despite a further period of conservative management, the patient failed to improve and was taken to the operating theater for a laparoscopic duodenojejunostomy.

The abdomen was entered through the umbilicus with an optiview port, and after insufflation of the abdomen, three 5-mm ports were inserted. The omentum was dissected away from the second and third parts of the duodenum, and it was observed that the stomach and duodenum were grossly distended with an associated collapsed small bowel distal to the duodenum. The transverse colon was elevated on sutures and a window was made lateral to the middle colic vessels to expose the duodenum. The duodenum was mobilized; the

Department of Upper GI Surgery, Concord Repatriation General Hospital, Sydney, New South Wales, Australia.

jejunum was approximated to the second part of the duodenum in a retrocolic fashion. A stay suture, incorporating the duodenum and the jejunum, was placed and enterotomies were made in both loops of bowel. A 45-mm staple gun was inserted, and a single fire was performed. Suture lines were hemostatic and intact, and the enterotomy was closed with a further staple line. There was no narrowing of the jejunal loop, which was left sitting in a satisfactory position. Operative time was 1 hour and 35 minutes. The patient recovered uneventfully and was discharged home on postoperative day 5. During the acute period prior to surgery, she lost 4 kg in weight, but this returned to 51 kg in 2 months postoperatively On follow-up, the patient has remained symptom-free 2.5 years postsurgery.

Case Report 2

A 28-year-old man was referred with a 10-year history of recurrent episodes of subumbilical pain, sweating, fullness, vomiting up to two meals at a time, weight loss of over 12 kg over 10 years, and explosive diarrhea. The episodes were becoming more frequent over the preceding 6 months. He had previously had multiple barium meal investigations that were inconclusive. Past medical history included a previous cholecystectomy. A CT scan with intravenous (i.v.) and oral contrast showed narrowing of the SMA/aortic angle to approximately 20 degrees. This was associated with a partial compression of the third part of the duodenum by the SMA. While no dilatation of the proximal duodenum was seen, the narrowing of the angle was in keeping with the suspected diagnosis of SMA syndrome. The patient underwent a laparoscopic duodenojejunostomy. The procedure was performed in the same fashion as described in the first patient. The operative time was 3.5 hours. The patient's recovery was uneventful, and he discharged himself 4 days postsurgery. On follow-up 5 years later, his symptoms have not recurred, and his weight had increased from 61 preoperatively to 75 kg.

Case Report 3

A 36-year-old man presented with a 13-year history of severe daily periumbilical abdominal pain, bloating, and flatulence, with occasional episodes of vomiting if the pain was prolonged. He had progressive weight loss because of poor intake due to postprandial pain and was 50 kg prior to surgery. He also complained of bowel changes between constipation and diarrhea. He had no medical history of note. Previous investigations under the care of his primary physicians included a hepatobiliary imino-diacetic acid scan, Meckel's scan, multiple gastroscopies, which included a bowel flush-out, and the introduction of new bowel flora for recolonization therapy. He was also treated with flagyl/salazopyrin and colchicine, which seemed to assist in managing the pain for a short period of time. He also underwent a negative diagnostic laparotomy. Due to persistent presentations, the patient underwent an abdominal CT scan that showed marked dilatation of the 2nd and 3rd parts of the duodenum and a tapering of contrast between the SMA and the aorta. The aorto-SMA angle was measured at approximately 17 degrees.

A diagnosis of SMA syndrome was made, and he was referred to our unit for consideration of laparoscopic duodenojejunostomy. At surgery, adhesions from the previous laparotomy were taken down, and findings included a grossly dilated 2nd and 3rd part of the duodenum and a completely collapsed 4th part of the duodenum with constrictions from the superior mesenteric vessels. The very short loop of upper jejunum was brought across the duodenum in the third part, and a stapled side-to-side anastomosis was performed. The remaining enterotomy was closed with 3/0 prolene. The procedure time was 2 hours. The patient was discharged on day 4. Since his operation 7 years ago, the patient has gained significant weight to approximately 62 kg. His symptoms, although not completely resolved, are significantly less severe. His persistent symptoms include bloating and flatulence, as well as alternating bowel habit, and are thought to be irritable bowl syndrome. However, his pain has resolved. On follow-up gastroscopies, he has had a widely patent duodenojejunostomy.

Discussion

SMA syndrome is defined as a compression of the third part of the duodenum between the superior mesenteric neurovascular bundle anteriorly and the aorta or vertebral column posteriorly. Compression of the duodenum is thought to occur due to loss of fat around the superior mesenteric neurovascular pedicle. SMA syndrome was first described in 1861 by von Rokitansky,[1] followed not long after by Willet, who described, in 1878, a 17-year-old male with similar symptoms after being placed into a body cast and hence coined the term "cast syndrome."[2] In 1927, Wilkie also changed the terminology to follow his surname after collating the largest series of patients with a chronic duodenal ileus.[3] The term has changed over the years, with Cimmino in 1961 describing it as an angioneuromesenteric occlusion of the duodenum,[4] and in the 1970s, it was described as a vascular compression of the duodenum.[5]

Although the term SMA syndrome has changed over the years, the symptomatology has remained similar. This includes the description of postprandial pain, fullness, volu-

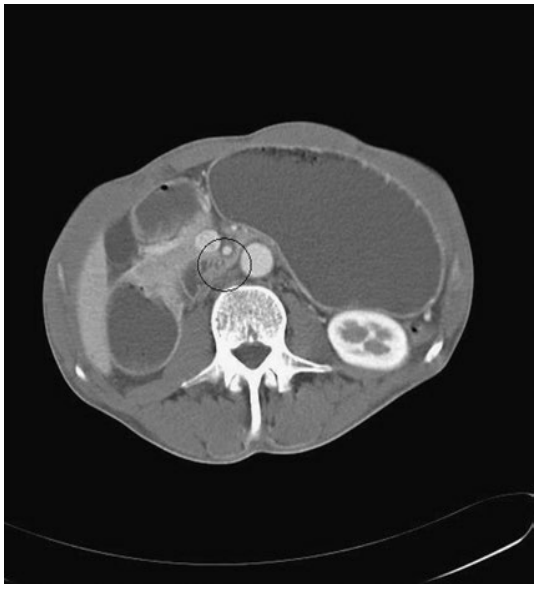


FIG. 1. Contrast computed tomography scan demonstrating dilated duodenum with transition point at level of superior mesenteric artery (circled).

minous vomiting, with early satiety, nausea, and weight loss.[5–10] The presentation may be of an acute nature within hours or a chronic condition, which culminates in progressive symptoms and severity.[7,8,11,12] The patients are described as having some relief of their symptoms when they place their knees to their chest or when lying in the prone position postprandially.[6] There has been a reported association of 25–45% and 50% with peptic ulcer disease and hyperchlorhydria, respectively.[8]

There are many thoughts as to the mechanism and cause of SMA syndrome. It is believed that a decrease in the aortomesenteric angle is one of the main contributing factors.[4,5,7,13–16] The SMA usually forms an angle of approximately 45 degrees (range, 38–56) with the abdominal aorta, and the 3rd part of the duodenum crosses caudal to the origin of the SMA, coursing between the SMA and aorta. Any factor that sharply narrows the aortomesenteric angle to approximately 6–25 degrees can cause entrapment and compression of the third part of the duodenum as it passes between the SMA and aorta, resulting in SMA syndrome. In addition, the aortomesenteric distance in SMA syndrome is decreased to 2–8 mm (normal is 10–20 mm).

This occurs either by reduction in the mesenteric fat, by chronic immobilization in the supine position, which can occur in trauma or burns patients,[7,17] or dietary disorders, such as anorexia nervosa or malabsorptive conditions.[1,10,18–20] Another factor considered to be involved is a thickening of the root of the mesentery itself. This may be due to the inflammatory pathology of a nearby structure, which affects the surrounding mesentery, such as episodes of acute pancreatitis, acute enterocolitis, bowel infarction, or cholecystitis.[8,11,14] Processes that limit the space of the vascular angle, such as tumors, lymph nodes, or abdominal aneurysms, can also result in the syndrome.[5,7,11,14] Diseases of the duodenum subsequently leading to thickening may also be involved, such as peptic ulcer disease and Crohn's disease.[10,14] Last, decreased intestinal motility, leading to atonia and dilatation of the lumen of the viscera, can be associated with SMA syndrome.[14]

As the diagnosis is essentially one of exclusion, frequently patients undergo multiple tests before a diagnosis is finally made.[16,21–23] This is due to the variety of patient presentation, the rarity of the syndrome, and the fact that conventional investigations can commonly be negative. Confirmation usually requires a combination of radiologic and endoscopic investigations. A plain X-ray may indicate gastric dilatation.[11,14,16] A majority of patients will receive an endoscopy to rule out a mechanical cause. A positive barium study will show duodenal dilatation with retention of barium within the duodenum. It will also show characteristic vertical linear extrinsic pressure in the 3rd portion of the duodenum.[11,14,16,22,24] Hypertonic duodenography is also used to display the location of an obstruction with a dilated proximal duodenum and antiperistaltic waves in the dilated portion of the duodenum.[14,16,18,21] This can provide sufficient evidence for the diagnosis. Ultrasound or arteriography are used to visualize the angle of the SMA and the aortomesenteric distance.[14,22] In agreement with other studies, we have found that CT provides information not only on the affected portion of the duodenum, but also assists in the measurement SMA-aortic mesenteric angle (Fig. 1).[14,16,22]

Treatment usually begins with a conservative medical approach.[1,11,25–27] Symptoms can resolve with i.v. fluid replacement, nasojejunal feeding in order to bypass the area of narrowing, small liquid meals, prokinetic agents, or positioning the patient in a knee to chest position or prone after eating.[8] Surgical treatment of SMA syndrome is indicated when either conservative management fails or the condition is chronic.[11] In 1908, Stavely performed the first open duodenojejunostomy,[28] after which many of the surgical procedures were performed open, either proceeding to a gastrojejunostomy, duodenojejunostomy, or a ligation of the ligament of Treitz with the associated repositioning of the duodenum.[15,25] This surgery produced good results for the patient's symptoms. Studies have showed that the most successful surgical procedure was a duodenojejunostomy.[26,27] Presently, laparoscopic management of SMA syndrome is becoming a more popular alternative to open procedures.[10,12,15,25–27] We have identified 6 case reports of laparoscopic surgical intervention of SMA syndrome. In 1995, Massoud described 4 patients that were treated via ligation of the ligament of Treitz and reported a 75% success rate.[15] Gersin and Heniford were the first to describe the laparoscopic technique of duodenojejunostomy in 1998.[12] Other reports from Richardson and Surowiec,[10] Bermas and Fenoglio,[25] Kim et al.,[29] and Kingham et al.[30] have indicated that laparoscopic management is a safe alternative and that the procedure time is reduced, the operative field is adequately accessed and visualized, and recovery time is also reduced. As seen in our case series, all 3 patients were treated conservatively in the first instance, but due to persistent symptoms, underwent laparoscopic surgery. All 3 cases had minimal operating times, an uneventful recovery, and were discharged shortly after surgery. Two of the 3 patients had complete symptomatic relief and the third had a significant improvement.

Conclusion

We believe that laparoscopic duodenojejunostomy is the most appropriate form of surgical management in patients who have failed conservative medical management of their SMA syndrome.

Disclosure Statement

No competing financial interests exist.

References

1. von Rokitansky C. Lehrburch der Pathologischen Anatomie. Vienna, Austria: Braumuller and Seidel, 1861.
2. Willet A. Fatal vomiting following application of plaster of paris bandage in case of spinal curvature. St Barth Hosp Rep 1878;14:538–544.
3. Wilkie DP. Chronic duodenal ileus. Am J Med Sci 1927;17: 643–649.
4. Cimmino CU. Arteriomesenteric occlusion of the duodenum: An entitiy? Radiology 1961;76:828–829.
5. Akin JT, Jr., Gray SW, Skandalakis JE. Vascular compression of the duodenum: Presentation of ten cases and review of the literature. Surgery 1976;79:515–522.
6. Alabkari HA, Aljaroof AH. Superior mesenteric artery syndrome: Report of two patients and review of the literature. Ann Coll Surg (Hong Kong) 2003;7:55–60.
7. Baltazar U, Dunn J, Floresguerra C, et al. Superior mesenteric artery syndrome: An uncommon cause of intestinal obstruction. South Med J 2000;93:606–608.

8. Biank V, Werlin S. Superior mesenteric artery syndrome in children: A 20-year experience. J Pediatr Gastroenterol Nutr 2006;42:522–525.
9. Mansberger AR, Hearn JB, Byers RM, et al. Vascular compression of the duodenum. Emphasis on accurate diagnosis. Am J Surg 1968;115:89–96.
10. Richardson WS, Surowiec WT. Laparoscopic repair of superior mesenteric artery syndrome. Am J Surg 2001;181:377–378.
11. Ahmed AR, Taylor I. Superior mesenteric artery syndrome. Postgrad Med J 1997;73:776–778.
12. Gersin KS, Heniford BT. Laparoscopic duodenojejunostomy for treatment of superior mesenteric artery syndrome. JSLS 1998;2:281–284.
13. Altiok H, Lubicky JP, DeWald CJ, Herman JE. The superior mesenteric artery syndrome in patients with spinal deformity. Spine 2005;30:2164–2170.
14. Carbo AI, Sangster G, Gates T, D'Agostino H. Role of imaging in the diagnosis of the superior mesenteric artery syndrome. J La State Med Soc 2006;158:31–33.
15. Massoud WZ. Laparoscopic management of superior mesenteric artery syndrome. Int Surg 1995;80:332–327.
16. Neri S, Signorelli SS, Mondati E, et al. Ultrasound imaging in the diagnosis of superior mesenteric artery syndrome. J Intern Med 2005;257:346–351.
17. Gustafsson L, Falk A, Lukest PJ, Gamklou R. Diagnosis and treatment of superior mesenteric artery syndrome. Br J Surg 1984;71:499–501.
18. Adson DE, Mitchell JE, Trenker SW. The superior mesenteric artery syndrome and acute gastric dilatation in eating disorders: A report of two cases and a review of the literature. Int J Eat Disord 1997;21:103–114.
19. Agarwal T, Rockall TA, Wright AR, Gould SWT. Superior mesenteric artery syndrome in a patient with HIV. J R Soc Med 2003;96:350–351.
20. Raissi B, Taylor BM, Taves DH. Recurrent superior mesenteric artery (Wilkie's) syndrome: A case report. Can J Surg 1996;39:410–416.
21. Crowher MAA, Webb PJ, Eye-Brook IA. Superior mesenteric artery syndrome following surgery for scoliosis. Spine 2002; 27:E528–E533.
22. Lundell L, Thurlin A. Wilkie's syndrome—A rarity? Br J Surg 1980;67:604–606.
23. Murthi GVS, Raine PAM. Superior mesenteric artery syndrome in children. Scot Med J 2001;46:153–154.
24. Chiu HH, Chao CC, Mo LR. Gastrointestinal: Superior mesenteric artery syndrome. J Gastroenterol Hepatol 2004; 19:593.
25. Bermas H, Fenoglio ME. Laparoscopic management of superior mesenteric artery syndrome. JSLS 2003;7:151–153.
26. Hines JR, Gore RM, Ballantyne GH. Superior mesenteric artery syndrome. Diagnositic criteria and therapeutic approaches. Am J Surg 1984;148:630–632.
27. Kepros JP. Superior mesenteric artery syndrome after multiple trauma. J Trauma 2002;53:1028–1029.
28. Stavely AL. Acute and chronic gastromesenteric ileus with cure in a chronic case by duodenojejunostomy. Bull John Hopkins Hosp 1908;19:252.
29. Kim YI, Cho NC, Kim DS, Rhoe S. Laparoscopic duodenojejunostomy for management of superior mesenteric artery syndrome: Two case reports and a review of the literature. Yonsei Med J 2003;44:526–529.
30. Kingham TP, Shen R, Ren C. Laparoscopic treatment of superior mesenteric artery syndrome. JSLS 2004;8:376–379.

Address correspondence to:
Clive J. Kelty, MBChB, PhD, FRCSEd, FRCS (Gen Surg)
Department of Surgery
Doncaster Royal Infirmary
Armthorpe Road
Doncaster, DN2 5LT
United Kingdom

E-mail: clive.kelty@bigfoot.com

Surg Endosc (2005) 19: 589–593
DOI: 10.1007/s00464-004-8711-6

SURGICAL ENDOSCOPY
and Other Interventional Techniques

Does routine intraoperative cholangiography prevent bile duct transection?

E. Debru, A. Dawson, S. Leibman, M. Richardson, L. Glen, J. Hollinshead, G. L. Falk

Department of Upper Gastrointestinal Surgery, Concord Repatriation General Hospital, The University of Sydney, Hospital Road, Sydney, NSW, 2139, Australia

Received: 14 September 2004/Accepted: 26 October 2004/Online publication: 11 March 2005

Abstract
Background: The role of routine intraoperative cholangiography is controversial. The aim of this study was to assess the impact of routine intraoperative cholangiography on the incidence of common bile duct injuries, and to evaluate the operative outcome of laparoscopic cholecystectomy carried out in a major teaching hospital and review the literature.
Methods: Prospectively collected data on 3,145 laparoscopic cholecystectomies performed mainly by surgical trainees in the period 1990 to 2002 using routine intraoperative cholangiography with fluoroscopy were reviewed.
Results: The mean age of the study sample (65.6% male, 34.4% female) was 54 years, and 16.9% of the patients had clinical acute cholecystitis. The conversion rate to open cholecystectomy was 4.3%. Intraoperative cholangiography was attempted for 90.7% of the patients with a 95.9% success rate. Five patients (0.16%) had common bile duct injuries. Four injuries had occurred in the first 5 years. One injury (0.06%) had occurred after 1995. This injury was identified intraoperatively and repaired laparoscopically. Routine intraoperative cholangiography prevented one definite common bile duct transection.
Conclusions: In this series using routine intraoperative cholangiography, there was a low rate and severity of common bile duct injuries, with a high intraoperative recognition rate. There was no bile duct transection or major injury requiring common bile duct reconstruction. Although intraoperative cholangiography helped in the immediate identification of injuries and the institution of appropriate therapy, injury was not completely prevented.

Key words: Common bile duct injury — Intraoperative cholangiography — Laparoscopic cholecystectomy

Correspondence to: G. L. Falk

Common bile duct injury (CBDI) is a serious complication of laparoscopic cholecystectomy (LC) [5, 12]. The reported incidence is widely variable [7, 9]. Many authors reporting the early years of LC demonstrated a higher rate and greater severity of CBDI than with open cholecystectomy (OC) [3, 6, 7, 12, 14, 18, 21–23]. Over time, the rate of injury has declined to a level, according to many authors, still higher than that for OC [6, 9, 12, 21]. It is evident that the use of routine intraoperative cholangiography (IOC) decreased significantly with the advent of LC [4, 5, 11, 13]. The role of routine IOC during LC continues to be a point of debate [11, 12].

The majority of CBDIs are attributable mainly to misidentified anatomy of the biliary tract [2, 6, 7]. Proponents of routine IOC argue that it reduces the rate of CBDI and facilitates the early recognition and repair of such an injury with the best possible results [1, 5, 10, 12, 13, 17, 20, 21, 24]. However, opponents claim that IOC prolongs surgery and increases cost, and that a safe cholecystectomy can be performed without IOC [1, 8, 19, 25].

In this study we reviewed the outcome of LCs performed in the upper gastrointestinal unit of a large teaching hospital from the introduction of the procedure and evaluated the impact that a policy of routine IOC had on the incidence of CBDI.

Methods

Data was collected prospectively for 3,145 LCs performed in the period 1990 to 2002 using a standard proforma. Surgical trainees routinely performed the majority of these procedures under variable supervision depending on their experience. There was a long-standing policy of routine IOC with fluoroscopy from the era of OC. The procedure was performed using a four-port technique, with patients in either the supine or lithotomy position. Cholangiography was performed using the Concord Cholangiography Set (Wilson Cook Australia, 8 Mile Plain, Queensland, Australia) after a small incision was made in the proximal cystic duct. The operating surgeon interpreted the films, and an intraoperative radiologic opinion was requested only

Table 1. Laparoscopic cholecystectomy outcomes

	1990–1995 (n = 1,485) %	1996–2002 (n = 1,660) %	1990–2002 (n = 3,145) %	p Value[a]
Conversion to open	6.3	2.5	4.3	< 0.0001
Cholecystitis	16.4	17.5	16.9	0.437
Attempted cholangiography	87.7	93.4	90.7	< 0.0001
Cholangiography success	94.8	96.7	95.9	0.013
Unsuspected stones	3.8	1.2	2.4	< 0.0001
Bile duct injury	0.27 (n = 4)	0.06 (n = 1)	0.16 (n = 5)	0.307

[a] Comparing 1990–1995 and 1996–2002

Table 2. Injury type and patient characteristics

Injury type	Year	Age (years)	IOC Dx	Hospital Stay (days)	Risk
Clip to CBD	1991	72	Yes	7	Dense adhesions
Lateral CBD	1993	70	Yes	13	Mirizzi, adhesions
Lateral CBD	1994	77	Yes	30	Gastrectomy
CBD stricture	1995	26	No[a]	11	Dense adhesions
CDCBDJ	2000	78	Yes	5	Difficult cannulation

IOC, intraoperative cholangiography; Dx, diagnosis; CBD, common bile duct; CDCBDJ, cystic duct CBD junction
[a] Presented 20 days later with cholangitis

rarely. The charts of all the patients with possible CBDI or abnormal cholangiographic findings and the charts of any whose procedure was converted to OC then were reviewed individually. The senior consultants of the unit were interviewed individually for any possible missed injuries. The patients identified with CBDI then were contacted for follow-up assessment.

The data were arbitrarily classified into two groups: 1990 to 1995 and 1996 to 2002. Differences between the two periods then were compared using the chi-square test, and p values less than 0.05 were considered significant.

Results

Overall, between 1990 and 2002, 3,145 cholecystectomies were performed (65.5% involving males and 34.4% involving females) (Table 1). The mean age was 54 years. There were operative findings of acute or chronic cholecystitis in 16.9% of all patients, but in 41% of those whose procedures were converted to OC. There was a total of five CBDIs (0.16%). Intraoperative cholangiography was helpful in making the diagnosis for 80% of the injuries. Four of the five injuries occurred in the first 5 years, and one injury occurred after 1995.

Injury types and relevant risk factors are summarized in Table 2. Difficult dissection was a major contributing factor for 80% of the injuries. One major transection was prevented as a clip was applied to a presumed cystic duct and an incision was made in the CBD for cholangiography. The incision was extended to extract a CBD stone and then closed over a T-tube (Table 3). A patient with a delayed stricture was admitted with cholangitis, then treated with endoscopic retrograde cholangiopancreatography (ERCP) and stenting. The stent was replaced once and an endoscopic dilation subsequently was performed once as a day procedure. Follow-up ERCPs have been normal. The three lateral injuries resulted in small leaks that were detected intraoperatively and easily repaired with a T-tube. One injury occurred after a persistent attempt to perform a cholangiogram and was treated with a laparoscopically placed T-tube. One patient had a prolonged hospital stay, which was largely because of nonmedical issues.

Table 3. Injury treatment and outcome

Injury	Treatment	Follow-up (2–8 years)
Clip to CBD	Clip removal, open T-tube	Deceased, unrelated cause
Lateral CBD	Open T-tube repair	Deceased, colon cancer
Lateral CBD	Open T-tube repair	Well
CBD stricture	ERCP + stent, balloon	Well
CDCBDJ	Laparoscopic T-tube	Well

CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; CDCBDJ, cystic duct CBD junction

Discussion

After the introduction and widespread application of LC, there was a considerable rise in iatrogenic CBDIs, which have declined with increased experience [5]. The hope that the injury rate would decline to that for OC has not been universally achieved [11, 12]. Archer et al. [1] have shown that surgical training is associated with fewer "learning curve" CBDIs, but that it has no effect on injuries occurring after 200 cases have been performed. A third of injuries occurred after the surgeon had performed 200 cases, leading to the conclusion that there is a risk inherent in the procedure.

From the largest population-based study in the literature, Flum et al. [5] showed a significant decrease in

Table 4. Studies with injury rates with and/or without cholangiography

Author	Total patients	Overall	CBD injury rate (%)		
			No IOC	Selective IOC	Routine IOC/with all
Ludwig [13]	95,363	0.32	0.34	0.30	0.28
Rosenthal [19]	71,991	0.37	0.37	0.42	0.30
Fletcher [4]	19186	0.23	0.36		0.14
Flum [6]	30,630	0.25	0.33		0.20
Flum [5]	1,570,361	0.50	0.58		0.39
Richardson [18]	5,913	0.60		0.60	
Macfadyen [14]	114,005	0.50		0.50	
Krahenbuh[9]	12,111	0.30		0.30	
Ludwig [12]	327,523	0.36		0.43	0.21

CBD, common bile duct; IOC, intraoperative cholangiography

the rate of CBDI with IOC after controlling for patient-level and surgeon-level factors (Table 4). In a meta-analysis of the literature, Ludwig et al. [12] found the rate of CBDI with LC to be 0.36%. With routine use of IOC, this rate was reduced to 0.21%, as compared to 0.43% when IOC was performed selectively. Fletcher et al. [4] reported similar findings of CBDI reduction with IOC. A comparison of injury rates by similar large studies in the literature showing a reduction in CBDI with IOC is summarized in Table 4. In the current study, the total CBDI rate of 0.16% is similar to the reported injury rate for OC [11, 12]. The rate has been shown to decrease from 0.27% to 0.06% after the first 5 years of "the learning curve." Other studies report comparable CBDI rates [2].

Another benefit of routine IOC is early recognition of injuries [11–13, 19, 23, 24]. The early diagnosis of CBDI significantly improves the clinical outcome and quality of life for patients, reduces total costs, and shortens the hospital stay [10, 20, 21]. However, Slater et al. [21] cautioned that this benefit is dependent on the surgeon's correct interpretation of the biliary anatomy displayed by the IOC. In the review by Ludwig et al. [12], the intraoperative diagnostic rate of injuries was 87% with routine IOC, as compared to 44.5% with selective IOC.

In our study, four of the five injuries were identified intraoperatively, and the appropriate treatment was instituted immediately. The hospital stay of the patients was not different from that for the average OC. One elderly patient had a prolonged stay for nonmedical reasons. The only incident not discovered intraoperatively was the delayed presentation of a stricture likely attributable to an ischemic cause.

There is some evidence that the injuries sustained during routine IOC are of lesser severity [11, 19, 21]. In the current series, in addition to the low rate, the injuries were of much lower severity. The "classic injury" of the CBD associated with LC and its variants have been well described (Fig. 1) [15, 23]. Because the most common cause of injury is misidentification of the CBD for the cystic duct, cholangiography would detect the mistaken incision in the CBD for cholangiography early and prevent complete transection or excision [2, 3, 10, 16, 17]. The first patient in our series would have undergone a definite bile duct transection had routine cholangiography not been performed. All other injuries were lateral injuries that were repaired with T-rube placement. These would be classified as Strasberg "D type" injuries, which are considered minor (Fig. 1) [23]. Given the considerable experience with laparoscopic CBD exploration in the unit, the latest injury was easily repaired over a T-tube laparoscopically, and the patient was discharged home in 5 days.

One of the arguments against routine IOC is that it adds unnecessary cost and time and is impractical. Intraoperative cholangiography adds an average of 8 min to the operative time [11]. In the current series, IOC required an extra 3 to 6 min. We have found that once the operating room team gets the message that this is an essential procedure required with every LC, the efficiency improves dramatically. The surgical trainees quickly grasp both the technique and the interpretation of cholangiography. Cost benefit analysis shows that the extra cost incurred by routine IOC is offset by savings on the cost of managing CBDI and possible litigation [1, 11, 16, 17]. According to Ludwig et al. [11], one severe CBDI prevented would potentially pay for 1,000 "unnecessary" cholangiograms.

Although clinically significant complications directly attributable to laparoscopic IOC are rare, the procedure is not completely benign [16]. For those not familiar with the interpretation of IOC, avoidable false-positive results for stones may lead to unnecessary CBD exploration or ERCP [16]. This goes against the argument for selective IOC. It is, however, important to note that one of the injuries we report was a leak at the cystic-duct-CBD junction resulting from a persistent attempt at cholangiography.

Although cognizant of the limitations of population-based retrospective studies, several large reports give similar results in favor of routine IOC (Table 4). Flum et al. [5] raises an important issue in suggesting that surgeons who perform routine IOC may be different in other ways that offer protection from CBDI. We speculate that performance of routine IOC may lead to a different technique of dissection with a focus on Hartmann's pouch-cystic duct junction, inadvertently leading to a safer "gallbladder down" process of dissection rather than a direct Calot's triangle-focused dissection. This is in fact what surgeons do when faced with severe inflammation during acute cholecystitis.

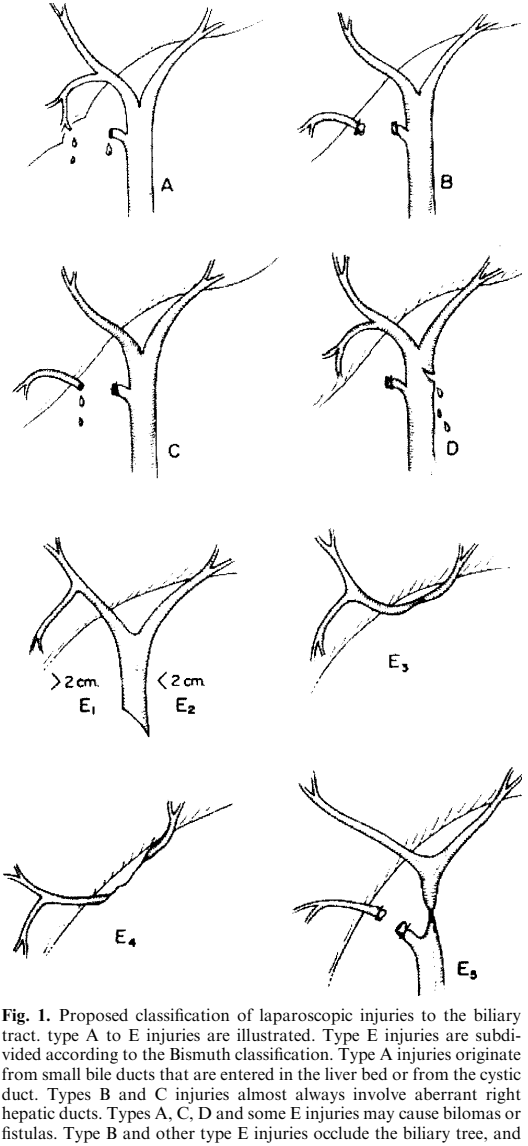


Fig. 1. Proposed classification of laparoscopic injuries to the biliary tract. type A to E injuries are illustrated. Type E injuries are subdivided according to the Bismuth classification. Type A injuries originate from small bile ducts that are entered in the liver bed or from the cystic duct. Types B and C injuries almost always involve aberrant right hepatic ducts. Types A, C, D and some E injuries may cause bilomas or fistulas. Type B and other type E injuries occlude the biliary tree, and bilomas do not occur. (Reprinted with permission, Strasberg et al. [23])

In conclusion we support the statement of Slater et al. [21] that IOC should not be a substitute for careful dissection and delineation of the anatomy. However it was evident in this study that IOC can be instrumental in the early recognition of injuries and avoidance of the sequelae associated with late diagnosis. It spared one patient a definite bile duct transection. In addition, the injuries sustained were of much less severity. Our experience shows that IOC is a technique that can be incorporated easily into the LC procedure, and when used routinely, can be performed efficiently. The findings also show that the risk of misinterpretation and complication is minimal.

Acknowledgment. The authors thank Debra Shearer for her help with data collection.

References

1. Archer SB, Brown DW, Smith CD, Branum GD, Hunter JG (2001) Bile duct injury during laparoscopic cholecystectomy: results of a national survey. Ann Surg 234: 549–558, discussion 558–559
2. De Wit LT, Rauws EA, Gouma DJ (1999) Surgical management of iatrogenic bile duct injury. Scand J Gastroenterol Suppl 230: 89–94
3. Deziel DJ, Millikan KW, Economou SG, Doolas A, Ko ST, Airan MC (1993) Complications of laparoscopic cholecystectomy: a national survey of 4,292 hospitals and an analysis of 77,604 cases. Am J Surg 165: 9–14
4. Fletcher DR, Hobbs MST, Tan P, Valinsky LJ, L. HR, Pikora TJ, Knuiman MW, Sheiner HJ, Edis A (1999) Complications of cholecystectomy: risks of laparoscopic approach and protective effects of operative cholangiography: a population-based study. Ann Surg 229: 449–457
5. Flum DR, Dellinger EP, Cheadle A, Chan L, Koepsell T (2003) Intraoperative cholangiography and risk of common bile duct injury during cholecystectomy. JAMA 289: 1639–1644
6. Flum DR, Koepsell T, Heagerty P, Sinanan M, Dellinger EP (2001) Common bile duct injury during laparoscopic cholecystectomy and the use of intraoperative cholangiography: adverse outcome or preventable error? Arch Surg 136: 1287–1292
7. Gouma DJ, Obertop H (2002) Management of bile duct injuries: treatment and long-term results. Dig Surg 19: 117–122
8. Hugh TB (2002) Laparoscopic bile duct injury: some myths. ANZ J Surg 72: 164–167
9. Krahenbuhl L, Sclabas G, Wente MN, Schafer M, Schlumpf R, Buchler MW (2001) Incidence, risk factors, and prevention of biliary tract injuries during laparoscopic cholecystectomy in Switzerland. World J Surg 25: 1325–1330
10. Kullman E, Borch K, Lindstrom E, Svanvik J, Anderberg B (1996) Value of routine intraoperative cholangiography in detecting aberrant bile ducts and bile duct injuries during laparoscopic cholecystectomy. Br J Surg 83: 171–175
11. Ludwig K, Bernhardt J, Lorenz D (2002) Value and consequences of routine intraoperative cholangiography during cholecystectomy. Surg Laparosc Endosc Percutan Tech 12: 154–159
12. Ludwig K, Bernhardt J, Steffen H, Lorenz D (2002) Contribution of intraoperative cholangiography to incidence and outcome of common bile duct injuries during laparoscopic cholecystectomy. Surg Endosc 16: 1098–1104
13. Ludwig K, Lorenz D, Koeckerling F (2002) Surgical strategies in the laparoscopic therapy of cholecystolithiasis and common duct stones. ANZ J Surg 72: 547–552
14. MacFadyen BV Jr, Vecchio R, Ricardo AE, Mathis CR (1998) Bile duct injury after laparoscopic cholecystectomy: the United States experience. Surg Endosc 12: 315–321
15. Martin RF, Rossi RL (1994) Bile duct injuries: spectrum, mechanisms of injury, and their prevention. Surg Clin North Am 74: 781–803
16. Millat B, Deleuze A, de Saxce B, de Seguin C, Fingerhut A (1997) Routine intraoperative cholangiography is feasible and efficient during laparoscopic cholecystectomy. Hepatogastroenterology 44: 22–27
17. Pondos YD, Gelfand DV, Dulkanchainun TS, Wilson SE, Cao S, Ji P, Ortiz JA, Imagawa DK (2001) Is intraoperative cholangiography during laparoscopic cholecystectomy cost effective?. Am J Surg 182: 663–669
18. Richardson MC, Bell G, Fullarton GM, WoSLCA Group (1996) Incidence and nature of bile duct injuries following laparoscopic cholecystectomy: an audit of 5,913 cases. Br J Surg 83: 1356–1360
19. Rosenthal RJ, Steigerwald SD, Imig R, Bockhorn H (1994) Role of intraoperative cholangiography during endoscopic cholecystectomy. Surg Laparosc Endosc 4: 171–174

20. Savader SJ, Lillemoe KD, Prescott CA, Winick AB, Venbrux AC, Lund GB, Mitchell SE, Cameron JL, Osterman FA (1997) Laparoscopic cholecystectomy-related bile duct injuries: a health and financial disaster. Ann Surg 225: 268–273
21. Slater K, Strong RW, Wall DR, Lynch SV (2002) Iatrogenic bile duct injury: the scourge of laparoscopic cholecystectomy. ANZ J Surg 72: 83–88
22. Strasberg SM (1997) Cholelithiasis and acute cholecystitis. Bailliers Clin Gastroenterol 11: 643–661
23. Strasberg SM, Martin H, Soper NJ (1995) An analysis of the problem of biliary injury during laparoscopic cholecystectomy. J Am Coll Surg 180: 101–125
24. Vecchio R, MacFadyen BV, Ricardo AE (1998) Bile duct injury: management options during and after gallbladder surgery. Semin Laparosc Surg 5: 135–144
25. Wright KD, Wellwood JM (1998) Bile duct injury during laparoscopic cholecystectomy without operative cholangiography. Br J Surg 85: 191–194

Excerpta Medica

The American Journal of Surgery

The American Journal of Surgery 187 (2004) 226–229

Laparoscopy

Teon pledget reinforced fundoplication causes symptomatic gastric and esophageal lumenal penetration

Elizabeth Dally, B.Med.[a,b], Gregory L. Falk, M.B.B.S.[a,b,*]

[a]*Department of Surgery, Concord Repatriation General Hospital, Concord, New South Wales, Australia*
[b]*Stratheld Private Hospital, Suite 2, Medical Centre, 3 Everton Rd., Stratheld, New South Wales, 2135 Australia*

Manuscript received January 27, 2003; revised manuscript June 8, 2003

Abstract

Background: Nissen fundoplication has become the standard operative procedure for the treatment of severe gastroesophageal reux disease. The use of Teon pledgets in Nissen fundoplications by our unit has been associated with a number of complications that has led to a change of technique in performing these operations.
Methods: We reviewed our database of all patients who had fundoplications that involved the use of pledgets and identied those who had represented with postoperative complications related to pledget erosion/migration.
Results: We identied 11 patients to date from a total of 1,175 fundoplications who had symptomatic pledget erosion occurring between 2 and 85 months after surgery (mean time 33.3 months). Symptoms included dysphagia, recurrent symptomatic gastroesophageal reux, chest pain, and melaena, and in some cases signicant morbidity was associated with the erosion. No common factor predisposing these patients to pledget erosion was identied. In the majority of cases removal of the pledget was associated with resolution of the symptoms. A review of the literature does not reveal any similar studies but problems associated with the erosion and migration of Teon prostheses are described.
Conclusions: The use of Teon pledgets in fundoplication is associated with a small but signicant risk of complications that has led to our unit abandoning this technique.

Keywords: Fundoplication; Teon; Pledget; Erosion; Esophagogastric penetration; Gastroesophageal reux

Nissen fundoplication (laparoscopic or open) has become the standard surgical treatment for severe gastroesophageal reux disease [1–6]. Complications of both the open and laparoscopic techniques have been well reported in the literature [7–11]. We have previously described a case in which the Teon pledgets used to buttress the wrap, eroded into the esophagus resulting in signicant morbidity [12]. The aim of this study was to investigate the incidence of this complication in our patient population and document the associated symptomatology and morbidity. All fundoplications performed by our unit between 1992 and 2000 involved the use of Teon pledgets. A review of our database has revealed that from a total of 1,175 operations there have been 11 cases where use of the Teon has resulted in the same problem as our initial case study. A review of the literature has not revealed similar cases.

Methods

A prospective computer based record has been kept of all patients operated on by the senior author; patient details being recorded by a data manager on a Microsoft database and Excel spreadsheet. All fundoplications both laparoscopic and operation are recorded individually. Hospital operation records were also reviewed for each case. A review of the literature using the Medline and Pub Med search engines was conducted, using the terms “fundoplication, postoperative complications, pledget, suture techniques, Teon, PTFE (polytetrauoroethylene), erosion, foreign body migration and inammation,” to identify any related case reports or articles.

* Corresponding author. Tel.: +612-9745-1099; fax: +612-9745-1299.
E-mail address: glf@tpg.com.au

0002-9610/04/$ – see front matter
doi:10.1016/j.amjsurg.2003.11.028

Results

Symptomatic lumenal penetration of Te on pledgets to this date has occurred in 11 patients from a total of 1,175 cases in our database, (an incidence of less than 1%). Patients suffering the complication ranged in age from 41 to 74 years with an average age of 55.8 years. There were 6 men (average age 53.2 years) and 5 women (average age 58.8 years). No common factor predisposing these patients to pledget erosion was identi ed.

Indications for initial surgery

All patients initially presented with symptoms of severe gastroesophageal re ux disease, incompletely controlled with medical therapy. Hiatus hernias were present in 4 of the 11 patients, grade 2 esophagitis in 6, Barrett's esophagus in 2, and esophageal stricture in 1. Two patients had had previous hiatal surgery, 1 a previous fundoplication with recurrent symptoms and a recurrent hiatus hernia, and the other a previous fundoplication and highly selective vagotomy. All patients had evidence of gastroesophageal re ux disease documented by endoscopy and either manometry and pH testing, or contrast radiology before their surgery.

Operations

Laparoscopic fundoplication was performed in 7 patients, 1 underwent a laparoscopic fundoplication and cut collis gastroplasty, and the 2 patients with previous surgery had open fundoplications, 1 with esophageal lengthening. The remaining patient underwent an open fundoplication because of multiple previous open abdominal operations.

In the immediate postoperative period 1 patient had problems with vomiting, and a super cial wound infection. The uncomplicated laparoscopic cases were discharged 2 to 3 days postoperatively and the open cases between 7 to 10 days. There was no difference between the series and subject patients in indication, operation or complications.

Outcome

Postoperatively all initially had good relief of heartburn and regurgitation. At the postoperative consultation 3 patients had a Visick score of 1, another 7 patients had a score of 2, and the remaining patient had a score of 3. Asymptomatic patients with no past diagnosed Barrett's esophagus are not routinely endoscopied after 3 months. All symptomatic patients, however, are routinely endoscopied. Symptoms recurred between 2 and 85 months after surgery (mean 33.3 months), with 36% of patients presenting more than 52 months after surgery (see Table 1). Also of note, however, is that fact that 5 of the 11 patients had had other ongoing problems between their initial surgery and further presentation with symptoms presumably related to their pledget erosion (eg, gastric ulceration, right upper quadrant pain, presumed biliary colic, atypical chest pain). Four patients underwent laparoscopic cholecystectomy for pains similar to biliary colic during the intervening period with 3 experiencing some relief of these symptoms. Uncertainty remains as to whether in ammation associated with early pledget erosion may have been responsible for some of this symptomatology, which was wrongly attributed to other causes.

Table 1
Time after initial surgery until symptomatic representation and diagnosis (months)

	Time to representation	Time to diagnosis of erosion
Mean	33.3	37.9
Median	24	37
Range	2–85	2–85

Representation

Symptoms that led to representation were varied. Three patients had dyspeptic epigastric pain and a recurrence of their initial symptoms of gastroesophageal re ux disease. Three had atypical chest pain (1 also with recurrent symptoms of gastroesophageal re ux disease), 2 had signi cant dysphagia (1 being the original patient) [12], and 3 presented with melaena and a signi cant drop in their haemoglobin. One of these latter patients, however, had already had a diagnosis of pledget erosion made on surveillance endoscopy for Barrett's, and was being managed medically prior to the bleed (see Table 2).

Patients with melaena underwent endoscopy which demonstrated the pledget erosion to be the source of the bleeding. The patients with dysphagia were investigated with a combination of barium swallow and gastroscopy, while those who presented with recurrent symptoms of gastroesophageal re ux disease were investigated with either contrast radiology, manometry and pH testing, and gastroscopy (or combinations of the above). Those who presented with atypical chest or epigastric pain, differing in nature to their previous symptomatic gastroesophageal re ux, were initially investigated for other causes of upper abdominal pain. This included abdominal ultrasonography and CCK/HIDA scans to exclude cholelithiasis as a cause. They were also investigated for recurrent gastroesophageal re ux disease.

Table 2
Symptoms at representation

Atypical chest pain	Predominant gastroesophageal re ux	Dysphagia	Melaena
3	3	2	3

Diagnosis

The diagnosis was made at gastroscopy in 9 of the 11 patients, during open surgery in 1, and during an endoscopic retrograde cholangiopancreatogram in the remaining patient. Eight patients had 2 or more gastroscopies before the diagnosis was con rmed and the pledgets successfully removed, with 2 patients having 4 gastroscopies each. Diagnosis was made between 2 and 85 months after the original surgery (mean 37.9 months). In 6 patients the diagnosis was made within 1 month of representation, in another 3 it took up to 6 months, and in the remaining 2, it took 18 months (see Table 1). In 5 cases the pledget had eroded into the stomach, in 4 the pledget had eroded into the cardioesophageal junction, and in the remaining 3 the pledget had eroded into the esophagus. Three patients also had recurrent hiatus hernias, and 1 had evidence of a gastroesophageal stula on contrast radiology.

Management

In 8 patients the pledgets were successfully removed by endoscopy (with 1 being during the abovementioned endoscopic retrograde cholangiopancreatogram). In 2 cases the pledgets were only removed at laparotomy, and 1 patient has a pledget that is yet to be removed (now 4 months after the diagnosis of pledget erosion). Removal of the pledget was performed at the time of diagnosis in 6 patients, within 2 months in 3 patients, and after 14 months in the other.

Symptoms resolved in 6 patients after endoscopic/open removal of the pledget with the period of follow-up ranging from 6 weeks to 34 months. After reoperative fundoplication a further 2 patients also had improvement of their symptoms. Two patients have continuing symptoms probably not attributable to the pledget erosion, 1 having right upper quadrant pain, and the other con rmed biliary pain and biliary dyskinesia.

Literature search

A review of the literature using the Medline and Pub Med search engines and the terms Te on, PTFE, pledget, erosion, fundoplication (laparoscopic and open), and complication does not reveal any other reports of postoperative erosion associated with Te on pledgets complicating fundoplication apart from our original patient [12]. Postoperative esophageal erosion or gastric ulceration is described in a small number of case reports, but the association with Te on pledgets is not described [11,13,14].

Multiple papers looking at the effectiveness and complications associated with both open and laparoscopic fundoplications did not mention any Te on-associated perforations [3–11]. Hinder et al [6] reviewed the effectiveness in 198 patients of laparoscopic fundoplication with pledgets being used to secure the wrap. During a follow-up period of up to 32 months, no complications associated with erosion of the pledgets were documented in this study population. A more recent paper by Bammer and Hinder et al [8] then looked at the 5- to 8-year follow-up of laparoscopic fundoplication in 171 patients. In this patient population again there is no mention of Te on-associated gastroesophageal perforation [8]. An earlier paper by Dunnington and DeMeester [9] looking at the 2-year follow-up of open fundoplications in 58 patients also mentions no problems associated with pledget erosion.

A review of the available literature looking for complications associated with the use of Te on in general, (using the words Te on, PTFE, erosion, foreign body migration, complication and immune reaction) reveals a small number of papers describing the erosion or migration of polytetra- uoroethylene pledgets, vascular grafts or implants [15–17]. One in particular described the erosion by pledgets originally used to close the aortic cannulation site in cardiac bypass surgery through the sternum, from whence they were extruded 6 years after the original operation [15]. Another describes the erosion into the urethra of a polytetra uoroethylene suburethral sling [16], and others describe the erosion into the small bowel of a polytetra uoroethylene venous grafts causing bowel obstruction [17]. Several authors describe the migration of Te on paste particles originally used to treat ureteric re ux, which then appeared elsewhere in the body [18–22].

A search looking for studies that speci cally investigated the safety of exogenous implant substances found a number of papers describing chronic, low-grade local in ammatory reactions to Te on implants [23–26]. It has also been shown to have the potential to migrate away from the initial site of insertion [27]. In general, however, it has been regarded as a largely inert substance less likely to cause problems than many others.

Comments

The Te on pledget buttressed fundoplication was performed with the view to prevent recurrence by reinforcing the wrap using a modi cation of the technique described in the literature by DeMeester [6]. An earlier paper by DeMeester [9] compared open fundoplication with medical treatment for gastroesophageal re ux and followed up 34 patients with pledget reinforced fundoplication for 2 years. No problems with pledget erosion were documented. Hinder et al [6] also used this technique in their study assessing the effectiveness of laparoscopic fundoplication in treating gastroesophageal re ux disease in 198 patients, although at 32 months they had not experienced any complications from pledget erosion.

In our experience the average time to representation with symptoms attributable to the pledget erosion was 33.3 months, and 36% of our patients presented only after 50 months. This longer period was a possible reason for the variance in observation between our ndings and those of

DeMeester [9] and Hinder et al [6]. In our experience the symptoms that led to representation were varied and often nonspeci c and insidious, resulting in the period between symptomatic presentation and the subsequent diagnosis of pledget erosion ranging from 0 to 19 months. Symptoms may be present many months before the pledget is visible on endoscopy, and, as in our series, these may be wrongly attributed to other causes. Bammer et al [8] noted that at long-term follow-up, 14% of their patients were on continuous proton pump inhibitor therapy, 79% of these for abdominal or chest symptoms thought to be unrelated to re- ux, and made the comment this was higher than expected. In only 6% was there documented gastroesophageal re ux disease and the others had "vague, nonspeci c symptoms" [8]. We consider that a proportion of these could be attributable to the effects of chronic in ammation associated with Te on pledgets.

Other reports of extrusion of Te on in different settings demonstrate the universal potential for this phenomenon [15–17]. In all cases the removal of the Te on (where possible) allowed resolution of the problem, as was found in this study in which 70% of patients experienced symptom resolution after removal of the pledget, and another 20% experienced signi cant improvement.

In conclusion, the use of Te on buttressed fundoplication has created an infrequent, but potentially dangerous situation not present using sutures alone. Te on appears to be not as "biologically inert" as previously assumed, and its use can lead to migration, implantation, and occasionally serious complications. In the face of the experience reported herein, we cannot support the use of this technique any further.

References

[1] The Department of Veterans Affairs Gastro-oesophageal Re ux Disease Study Group. Comparison of medical and surgical therapy for complicated gastro-oesophageal re ux disease in veterans. N Engl J Med 1992;326:786–92.

[2] Anvari M, Allen C, Borm A. Laparoscopic Nissen fundoplication is a satisfactory alternative to long-term omeprazole therapy. Br J Surg 1995;82:938–42.

[3] Allgood PC, Bachmann M. Medical or surgical treatment for chronic gastro-oesophageal re ux? A systematic review of published evidence of effectiveness. Eur J Surg 2000;166:713–21.

[4] Peters JH, DeMeester TR. Indications, bene ts and outcome of laparoscopic Nissen fundoplication. Dig Dis 1996;14:169–79.

[5] Peters JH, DeMeester TR, Crookes P, et al. The treatment of gastro-oesophageal re ux disease with laparoscopic Nissen fundoplication: prospective evaluation of 100 patients with "typical" symptoms. Ann Surg 1998;228:40–50.

[6] Hinder RA, Filipi CJ, Wetscher G, et al. Laparoscopic Nissen fundoplication is an effective treatment for gastro-oesophageal re ux disease. Ann Surg 1994;220:472–83.

[7] Lafullarde T, Watson DI, Jamieson GC, et al. Laparoscopic Nissen fundoplication. Five year results and beyond. Arch Surg 2001;136: 180–4.

[8] Bammer T, Hinder RA, Klaus A, Klingler PJ. Five to eight year outcome of the rst laparoscopic Nissen fundoplications. J Gastrointest Surg 2001;5:42–8.

[9] Dunnington GL, DeMeester TR. Outcome effect of adherence to operative principles of Nissen fundoplication by multiple surgeons. The Department of Veterans Affairs Gastroesophageal Re ux Disease Study Group. Am J Surg 1993;166:654–9.

[10] Viljakka MT, Luostarinen ME, Isolauri JO. Complications of open and laparoscopic antire ux surgery: 32 year audit at a teaching hospital. J Am Coll Surg 1997;185:446–50.

[11] Collet D, Cadiere GB. Conversions and complications of laparoscopic treatment of gastro-oesophageal re ux disease. The Formation for the Development of Laparoscopic Surgery for Gastro-oesophageal Re ux Disease Group. Am J Surg 1995;169:622–6.

[12] Baladas HG, Smith GS, Richardson MA, et al. Esophagogastric stula secondary to Te on pledget: a rare complication following laparoscopic fundoplication. Dis Esophagus 2000;13:72–4.

[13] Bianchi A, Ubach M. Giant gastric ulcer penetrating into the heart as a late complication of Nissen fundoplication. Eur J Surg 1991;157: 61–2.

[14] Wasvary H, Wease G, Bierema T, Glover J. Gastro-aortic stula: an uncommon complication of Nissen fundoplication. Am Surg 1997; 63:455–8.

[15] Conn KS, Dunning JJ, Pillai R. Extrusion of Te on aortic pledgets from a sternal wound six years after cardiac surgery. Eur J Cardiothorac Surg 1997;12:150–3.

[16] Cholhan HJ, Stevenson KR. Sling transection of urethra: a rare complication. Int Urogynecol J Pelvic Floor Dysfunct 1996;7:331–4.

[17] Jarrett F, Hirsch SA, Steed D, Boehnke M. Small-bowel obstruction caused by intralumenal migration of prosthetic grafts. J Vasc Surg 1985;2:477–9.

[18] Claes H, Stroobants D, Van Meerbeek J, et al. Pulmonary migration following periurethral polytetra uoroethylene injection for urinary incontinence. J Urol 1989;142:821–2.

[19] Steyaert H, Sattonnet C, Bloch C, et al. Migration of polytetra uoroethylene paste particles to the kidney after treatment for vesicoureteric re ux. Br J Urol Int 2000;85:168–9.

[20] Aaronson I, Rames R, Greene W, et al. Endoscopic treatment of re ux: migration of Te on to the lungs and brain. Eur Urol 1993;23: 394–9.

[21] Borgatti R, Tettamanti A, Piccinelli P. Brain injury in a healthy child one year after periureteral injection of Te on. Pediatrics 1996;98: 290–1.

[22] Dewan PA, Fraundorfer M. Skin migration following periurethral polytetra uorethylene injection for urinary incontinence. Aust NZ J Surg 1996;66:57–9.

[23] Aragona F, D'Urso L, Scremin E, et al. Polytetra uoroethylene giant granuloma and adenopathy: long-term complications following subureteral polytetra uoroethylene injection for the treatment of vesicoureteral re ux in children. J Urol 1997;158:1539–42.

[24] Galgut P, Waite I, Smith R. Tissue reactions to biodegradable and non-degradable membranes placed transcutaneously in rats, observed longitudinally over a period of 4 weeks. J Oral Rehab 1996;23:17–21.

[25] Noe HN, Williams RS, Causey J, Smith DP. Long-term effects of polytetra uoroethylene injected into the rat bladder submucosa. Urology 1994;43:852–6.

[26] Kossovsky N, Millett D, Juma S, et al. In vivo characterization of the in ammatory properties of poly(tetra uoroethylene) particulates. J Biomed Mater Res 1991;25:1287–301.

[27] Malizia AA, Reiman HM, Myers RP, et al. Migration and granulomatous reaction after periurethral injection of polytef (Te on). JAMA 1984;251:3277–81.

Diseases of the Esophagus (1998) **11**, 260–262

WORKSHOP

Laparoscopic cut Collis gastroplasty: a novel technique

G. L. Falk, R. I. Harrison

Division of Endosurgery, Department of Surgery, Concord Hospital, Sydney, Australia

INTRODUCTION

The surgical treatment of gastro-esophageal reflux disease has undergone a period of rapid change with the advent of laparoscopic techniques. Many series are reporting excellent early results.[1,2]

Patients with severe disease such as Barrett's esophagus, esophageal stricture or giant mixed hernias may present the technical difficulty of shortened esophagus. The complication of reherniation may relate to the presence of shortened esophagus.[3]

In the open era, an accepted method of managing the short esophagus has been the Collis gastroplasty.[4] This operation has often required thoracotomy. Martin et al.,[5] describe a simple technique, an adaptation of the Mason gastroplasty, which allows performance of this operation transabdominally.[6] We have adapted this technique to be performed by laparoscopy, and report the technique in three consecutive patients with shortened esophagus.

OPERATIVE TECHNIQUE

The usual five port approach to laparoscopic fundoplication is utilized.[7] Full hiatal and esophageal mobilization is performed. The short gastric vessels are divided and posterior gastric vessels, when present, are also divided. It has been our impression that the vision obtained by laparoscopy may be deceptive and a measured segment of 3 cm of intra-abdominal oesophagus (along the known length of a grasper) should be obtained.

Full mobilization of the hiatus and bare area of the stomach is performed. An assessment of the tension required to hold the cardio-esophageal junction 2 cm within the abdominal cavity is made. This is necessarily judgemental. If, after full mobilization, with no posterior attachments remaining, the cardio-esophageal junction cannot be delivered into the abdominal cavity with moderate retraction, we have considered the esophagus short.

Once short esophagus is diagnosed intraoperatively an 18 mm dilating trocar* is introduced in the mid clavicular line to the right of the umbilicus. The Stealth 21 ECS circular stapler* is introduced through the wound after the trocar is removed. The abdominal wall seals adequately around the stapler to maintain pneumoperitoneum. The anvil is removed within the abdominal cavity and the spike attachment placed in the anvil. A 44 French bougie is passed orally and positioned along the lesser curve of the stomach to calibrate the Collis tube, so excessive 'bagginess' of the lengthened esophagus is avoided. The fundus of the stomach is then elevated and a modified Allis laparoscopic clamp is used to grasp the anvil and spike while it is passed from posterior to anterior close alongside the bougie at the lesser curve. The spike is removed, anvil reattached to the ECS 21 and a stapled window made between anterior and posterior wall of the stomach. Occasional bleeding is suture ligated. The stapled tube is constructed by insertion of an endoscopic linear cutter alongside the bougie (Fig. 1).

The hiatal repair is performed around a 56 Fr bougie with O Ethibond* and a posterior 270 degree partial fundoplication completed using 2/0 Ethibond.* (Fig. 2). The fundoplication is sutured to the diaphragm laterally, and the crura posteriorly (fundophrenopexy). A partial fundoplication has been performed as the Collis tube is aperistaltic and the effect on swallowing was uncertain.

RESULTS

The procedure has been undertaken in three patients, all female, ages 44,57 and 86 years, weight 83 Kg, 83 Kg and 55 Kg. Two patients had large mixed hernias

Correspondence to: **Gregory L. Falk** MB BS FRACS, PO Box 1085, Strathfield, Sydney, Australia 2135.

*Ethicon Endosurgery: Johnson and Johnson Medical

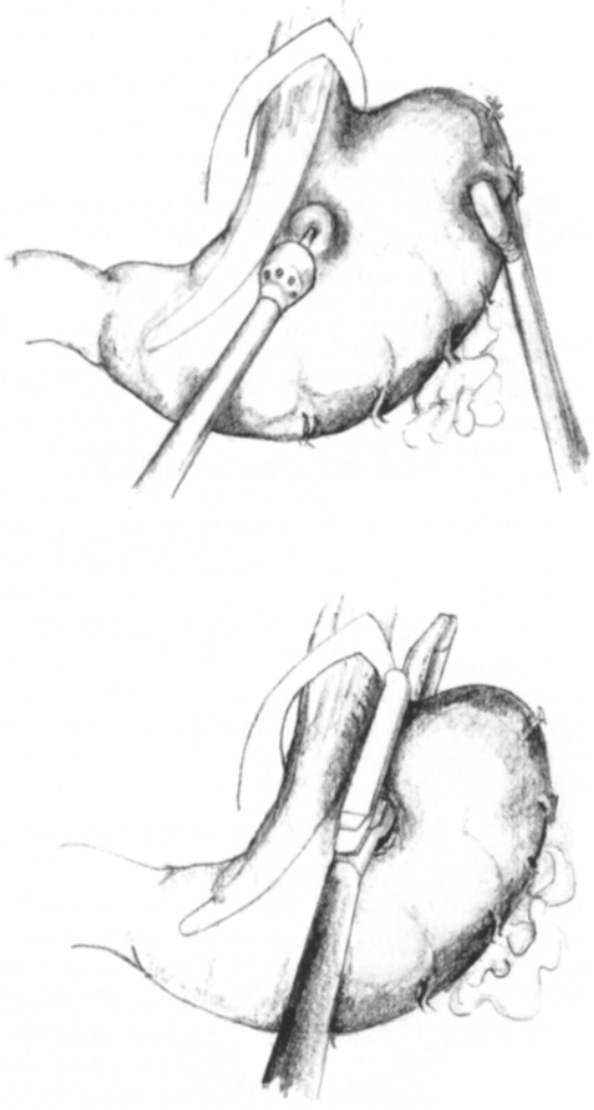


Fig. 1 Staplers for transabdominal cut-collis gastroplasty.

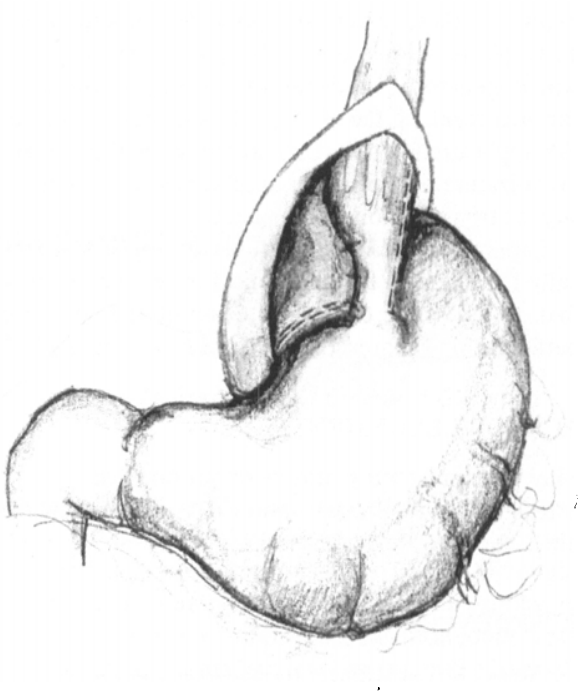


Fig. 2 Completed stapled cut-collis gastroplasty.

and one had a sliding hernia with previous stricture and the cardio-esophageal junction was 8 cm above the hiatus. All patients underwent preoperative manometry and 24 h esophageal pH studies. Acid exposures during the 24 h period were 6.9%, 7.3% and 14.2%. All patients had preoperative esophagitis and failed symptomatic control on proton pump inhibitors. The peristaltic function of all three patients was normal on manometry.

The operation in each case was undertaken using the previously described technique. The operation duration decreased progressively with familiarization from 240 min in the first case to 140 min in the third.

Postoperative management consisted of a 48 h total fast, then a contrast swallow prior to consuming oral fluids. Two patients were discharged well on day 5, and one on day 4, postoperatively. With further familiarity with the procedure a contrast swallow will be performed on postoperative day 1, planning for earlier discharge.

There were no postoperative complications and all three are symptomatically excellent 1, 2 and 3 months postoperatively. All are tolerating a normal diet. All patients have control of heartburn and regurgitation and one suffered mild transient dysphagia which has settled. Each patient has undergone a delayed Barium meal showing intact fundoplication and gastroplasty tube

DISCUSSION

This technique of laparoscopic transabdominal cut Collis gastroplasty has not been described before. Three cases of Collis gastroplasty have been successfully performed by Swanstrom,[3] where the stapling instrument has been introduced through the chest. Swanstrom and others report that it is possible some of the reported complications of laparoscopic fundoplication, such as acute paraesophageal hernia and hiatal failure may be related to undiagnosed short esophagus and may be avoided by judicious use of the laparoscopic Collis gastroplasty.[8–10]

It is our opinion that the use of the gastroplasty tube is only needed if full intrathoracic mobilization of the esophagus has failed to yield an adequate length of intraabdominal esophagus without undue tension. What constitutes undue tension is purely judgemental at this point. We have based identification of 'short' esophagus on operative findings at completion of dissection. Large hiatal herniation (> 5 cm), previous stricture and Barrett's esophagus alert us to the potential of 'short' esophagus, but

many of these cases are possible without Collis gastroplasty. Either our technique, or Swanstrom's, would seem to offer advantages, over open surgery, in the treatment of the shortened esophagus, however, the application of Martin's technique will allow full visualization of the stapler at all times, and no necessity for transgression of the pleura.

Laparoscopic Collis gastroplasty appears technically feasible and further clinical experience is justified, to assess the clinical outcome of the operation performed by laparoscopy.

ACKNOWLEDGEMENT

May we express our gratitude to our talented colleague, Mr R. Brancatisano FRACS who drew the illustrations for this manuscript.

REFERENCES

1. Weerts J M, Dallemagne B. Hanoir E et al. Laparoscopic Nissen Fundoplication: detailed analysis of 132 patients. Surg Endosc 1993; 3: 359–364.
2. Hinder R A, Filipi C J, Wescher G et al. Laparoscopic Nissen fundoplication is an effective treatment for gastrooesophageal reflux disease. Ann Surg 1994; 220: 472–481.
3. Swanstrom L L, Marcus D R, Galloway G W. Laparoscopic Collis Gastroplasty in the treatment of choice for the shortened oesophagus. Am J Surg 1996; 171: 477–481.
4. Collis J L. An operation for hiatus hernia with short oesophagus. Thorax 1957; 12: 181–188.
5. Martin C J, Strugnell N A. Double stapled abdominal Collis-Nissen operation: a simplified method. Aust NZJ Surg 1994; 64: 371–372.
6. Mason E E. Morbid Obesity: Use of vertical banded gastroplasty. Surg Clin North Am 1987; 67: 521–537.
7. Falk G L, Brancatisano R P, Hollinshead J W, Moulton J. Laparoscopic fundoplication: A Preliminary report of the technique and post operative care. Aust NZJ Surg 1992; 62: 969–972
8. Watson D I, Jamieson G G, Devitt P G et al. Para oesophageal hiatus hernia: An important complication of laparoscopic Nissen fundoplication. Br J Surg 1995; 82: 521–523.
9. Munro W, Brancatisano R, Adams I P, Falk G L. Complications of Laparoscopic Fundoplication: The first 100 patients. Surg Laparoscopy Endoscopy 1996; 6: 421–423.
10. Lim J K, Moisidis E, Munro W S, Falk G L. Reoperation for failed antireflux surgery. Aust NZJ Surg 1996; 66: 731–733.

A PRELIMINARY EXPERIENCE OF LAPAROSCOPIC CHOLEDOCHOTOMY WITH PRIMARY CLOSURE

Technique and results in 11 patients

R. I. Harrison, G. L. Falk

Sydney - Australie

The introduction of laparoscopic gallbladder surgery has raised new issues in the treatment of common bile duct (CBD) calculi. Surgeons have increasingly acquired the skills to remove CBD calculi by laparoscopy. The use of endoscopic retrograde cholangio-pancreatography (ERCD) and endoscopic sphincterotomy (ES) for preoperative diagnosis and management of CBD calculi based upon the "principal" of minimal invasion, became more prominent. This occurred despite complication rates of ES of around 10% [1, 2, 3]. *Complication rates, therefore, became cumulative as ERC and ES were combined with laparoscopic cholecystectomy rates that were similar to conventional surgical exploration of the CBD* [4, 5, 6]. *This is especially poignant in a group of patients in whom bile duct surgery had previously been relatively safe, namely the younger and healthier patients. Cognisant of these factors, our unit has been performing laparoscopic choledochotomy with fibreoptic cholangioscopy since 1991. Since that time 90 choledochotomies have been performed in the surgical unit and have been reported. It has been our practice to routinely place a T-tube into the CBD after completion of CBD exploration. Based upon results of both open and, more recently, laparoscopic primary CBD closures* [7, 8, 9] *we have undertaken a similar series since March 1996 and our experience with the first eleven patients is presented.*

KEY WORDS : **Laparoscopy, Common bile duct lithiasis, Choledocotomy, Laparoscopic primary closure.**

METHODS

The first patient was treated by primary CBD closure in March 1996. Since that time, 11 patients (F / M : 8/3) with average age 69 years have undergone similar laparoscopic treatment for choledocholithiasis.

SURGICAL TECHNIQUE

The patient can be positioned in either the "American" or "French" position with the surgeon standing on the patient's left side. Four ports are required routinely but a fifth port can be placed to enable downward retraction on the duodenum to expose the CBD.

Intraoperative cholangiogram is routine and confirms the presence and site of CBD stones. Laparoscopic choledochotomy is reserved for those patients that are deemed unsuitable for transcystic exploration ; namely, large and multiple CBD stones and proximal duct stones. We have elected not to explore a CBD less than 6 mm by laparoscopy.

A two handed scissor dissection technique is utilised to elevate the adventitia over the CBD. A "patch" of adventitia is excised from the anterior aspect of the CBD.

Choledochotomy is made using a sharp hook or cutting diathermy. Careful cautery of vessels is usually required. The length of choledochotomy is dictated by the size of the stone to be extracted but is, in principle, kept to a minimum. The flexible choledochoscope can be easily deployed via the epigastric port and guided by an overtube. Stones are extracted by Dormia retrieval, flushing, balloon or massage.

After choledochoscopy confirms duct clearance the choledochotomy is closed using a continuous 4/0 PDS① or Maxon② suture. We have used a size 4 end hole ureteric catheter inserted into the cystic duct and secured with a

LAPAROSCOPIC CHOLEDOCOTOMY WITH PRIMARY CLOSURE - 11 PATIENTS

	Presentation	Cholangiogram	Length of operation	Length of stay (Post op)	Complications	Follow up (months)
M 45	Elective surgery Normal LFT's & US	8 mm CBD Single distal stone	200 mins	2 days	Nil	9
F 77	Elective surgery Preop. US dilated duct	15 mm CBD Single stone	90 mins	4 days	Nil	9/12
F 79	Elective surgery Normal LFT's/US	10 mm CBD Single large stone	170 mins	3 days	Suspected pulmonary embolism stone month	8/12
F 61	Elective surgery Symptoms of cholangitis	10 mm CBD Multiple stones	240 mins	2 days		5/12
F 54	Elective surgery No symptoms	8 mm CBD Multiple stones	150 mins	3 days		5/12
F 54	Urgent admission Pancreatitis/ Cholangitis	12 cm CBD Large stone	160 mins		Died D4 pollop Asp Pneumonia	
F 72	Elective surgery Symptoms of cholangitis	12 mm CBD Single stone	160 mins	3 days		5/12
F 73	Elective surgery No symptoms	10 mm CBD Large stone	180 mins	6 days		4/12
F 79	Elective surgery No symptoms	15 mm CBD Large stone	120 mins	4 days	Superficial wound infection	4/12
M 51	Urgent admision Jaundice	10 mm CBD Large stone	190 mins	3 days		3/12
M 82	Urgent admission Cholangitis	15 mm CBD Stones	180 mins	4 days		2/12

Table I

springloaded clip (Allport[1]) to drain the duct. This has enabled both a vent for CBD drainage and provides an opportunity for cholangiography. A closed suction drain is placed to the gallbladder bed and subhepatic space.

Discharge is planned for Day 2 post surgery, with the biliary catheter on free drainage. The closed suction drain is removed if no evidence of bile leak has occurred. The ureteric catheter is removed at one week where, as an outpatient, the patient has a cholangiogram and, if clear, the catheter is removed under fluoroscopy to ensure no displacement of the springloaded clip.

❒ RESULTS

Most patients in this series are elderly, only 3 of the 11 patients being under the age of 60 years. In 7 patients, one could predict the presence of CBD stones on the basis of symptoms or on ultrasound findings of a dilated duct. Stones were found in the CBD by the policy of routine cholangiography, without clinical indicators (see table I). The median operative time was 160 minutes (90-240 mins range) and median length of stay of 3 post op days (2-6) days.

The single death in the series occurred in an 84 year old woman who was admitted from the Emergency Department with gallstone pancreatitis. She had a significant past history of ischemic heart disease. When the amylase had returned to normal the cholecystectomy and choledochotomy was performed taking 160 mins and with no apparent surgical problem. Post operatively she became

[1] *Ethicon Endo-Surgery*
[2] *Sherwood-Davis&Geck*

confused and required ongoing intravenous therapy and intensive nursing care. She regurgitated copiously on Day 4 and suffered a respiratory and subsequent cardiac arrest. Post mortem examination confirmed a large volume pulmonary aspiration and coronary vessel occlusion. The choledochotomy was intact and there was no bile collection.

A possible pulmonary embolism occurred in the 79 year old woman with longstanding steroid dependent chronic airways disease. She was readmitted one month post operatively with respiratory distress. Nuclear medicine scan indicated an intermediate probability of pulmonary embolism and duplex scan of both lower limbs revealed no evidence of deep vein thrombosis. She was electively anticoagulated and made a satisfactory recovery.

❒ DISCUSSION

Laparoscopic primary duct closure is not routine in clinical practice. There are a number of reasons for this. T-tubes have had a long history based upon the principle of decompressing the bile duct to avoid postoperative leakage after choledochotomy. It has had the added benefit of enabling ready access to the CBD for cholangiography and, if required access for retrieval of retained stones. However, it is well established that T-tubes are readily colonised and contribute to a higher rate of post operative bacteraemia than in studies of primary closure [8]. In these studies, overall morbidity rates are increased in those patients who have had a T-tube placed [7, 8]. In our own series, T-tubes have been associated with a significant risk of post operative cholangitis as well as implicated in bile leaks, biliary stricture and unexplained post operative sepsis [10]. No patient in this series had a post operative complication related to bile stasis, extravasation or sepsis. While the numbers are small, the absence of retained stones is encouraging and we consider is not in itself a reason to prophylactically use T-tubes.

The length of operating time and hospital stay are important issues in discussing the advantages and disadvantages of minimally invasive surgery. The increased operating time in performing laparoscopic choledochotomy can be explained by a number of technical factors. Precise dissection to expose a satisfactory segment of CBD is mandatory and the operating field is complicated by the addition of flexible choledochoscopy. Resuture of the duct is technically demanding. The median operating time of 160 minutes is similar to other series [9, 11, 12]. The median length of stay of 3 days compares favourably with other series [9, 11, 12, 13]. It represents a significant improvement in the choledochotomy and T-tube group of our first 50 whose average length of stay was 7 days and, clearly, is an improvement from the figures in the open exploration series [2, 4, 5, 6, 10].

The 84 year old woman who died following pancreatitis had associated co-morbidities that made her a significant operative risk, but because of good performance score was selected for surgery. Despite being managed in a high dependency suite she aspirated with ensuing hypoxia and cardiac arrest. We do not feel that her death was directly related to the new technique of laparoscopic exploration but rather to the use of surgery for her condition. Perhaps ERCP alone may have been less morbid.

This report details our early experience with an evolving technique of management of choledocholithiasis. We have been very encouraged with these results and feel that primary closure after choledochotomy is not only feasible, it may well be preferable to using the traditional technique of T-tube drainage. As in other reports, we support the principle of multi-institutional randomised trials to determine the optimal method of management of CBD calculus.

❒ CONCLUSION

While this report is preliminary and the number of procedures small, it is evident that satisfactory closure of the bile duct can be obtained.

Repatriation General Hosptial - Dpt of Surgery
Concord NSW 2139 Sydney - Australie

Correspondence :
Gregory L. Falk
P.O. Box 1085
Strathfield NSW 2135
Sydney - Austalie

SUMMARY

As a further advance in minimally invasive surgery of common bile duct stones, the authors report a small experience of choledochotomy and primary duct closure. The rational of this approach is to decrease the morbidity of the treatment of common bile duct calculi, and to avoid the significant complication rates (10%) of endoscopic sphincterotomy. The early results in 11 patients are reported, the technique outlined and the potential of the procedure discussed.

RÉSUMÉ

Comme une avancée suppléméntaire dans la chirurgie mini-invasive des voies bilaires, les auteurs rapportent une petite expérience de la cholédocotomie avec fermeture idéale du canal cholédocien. La raison de cette approche est de diminuer la morbidité dans le traitement de la lithiase des voies bilaires et d'éviter des taux de complications significatives (10%) de la sphinctérotomie endoscopique. Les résulats précoces chez 11 patients sont rapportés, les grandes lignes de la tehnique et le potentiel de la procédure discutés.

Depuis mars 96, 11 patients porteurs de lithiase de la voie biliaire principale ont été traités par cholédocotomie laparoscopique avec fermeture immédiate de la voie biliaire principale. Il s'agissait de 8 femmes et 3 hommes avec un âge moyen de 69 ans. La cholédocotomie ne s'adressait qu'aux cholédoques de diamètre supérieur à 6 mm. Une sonde urétérale taille 4 était laissée en place pour le cystique, fixée par un clip All Port. Le malade sortait à J2 avec le drain transcystique qui était enlevé à une semaine sous contrôle fluoroscopique après cholangiographie ; la durée opératoire moyenne a été de 160 minutes (20-240) et le séjour moyen de 3 jours (2-6). On déplore une suspicion d'embolie pulmonaire, 1 décès chez une défaillance polyviscérale, mais sans anomalie de la zone opératoire et une infection superficielle de paroi. Les auteurs pensent que la fermeture primitive du cholédoque doit être préférée au drain de Kerh lorsque cela est possible ; seules des études randomisées multicentriques permettront de conclure.

MOTS CLÉS : **Cœlioscopie, Lithiase de la voie biliaire principale, Cholédocotomie, Fermeture cholédocienne idéale.**

REFERENCES

1 - KORMAN J., COSGROVE J., FURMAN M., NATHAN I., COHEN J. : The role of endoscopic retrograde cholangiopancreatography and cholangiography in the laparoscopic era : *Ann. Chir., 1996, 223.2, 212-216.*

2 - STIEGMAN G., GOFF J., MANSOUR A., PEARLMAN N., REVEILLE R., NORTON L. : Precholecystectomy endoscopic cholangiography and stone removal is not superior to cholecystectomy, cholangiography and common duct exploration : *Ann. J. Surg., 1992, 163, 227-230.*

3 - GRAHAM S., FLOWERS J., SCOTT T., BAILEY R. SCOVILL W., ZUCKER K., IMBEMBO A. : Laparoscopic cholecystectomy and common bile duct stones : *Ann. Surg., 1993, 218, 1, 61-67.*

4 - MOREAUX J. : Traditional surgical management of common bile duct stones : A prospective study during a 20 year experience : *Ann. J. Surg., 1995, 169, 220-226.*

5 - MORGANSTERN L., WONG L., BERCI G. : Twelve hundred open cholecystectomies before the laparoscopic era. A standard for comparison : *Arch. Surg., 1992, 127, 400-403.*

6 - SCHWAB G., POINTNER R., WESTSCHER G. : Treatment of calculi of the common bile duct : *Surg. Gynecol. Obstet., 1992, 175, 115-120.*

7 - COLLINS P. : Further experience with common bile duct future without intraducted drainage following choledochotomy : *Br. J. Surg., 1967, 54, 854-856.*

8 - LYGIDATIS N. : Choledochotomy for Biliary Lithiasis : T-tube drainage or primary closure : *Ann. J. Surg., 1983, 146, 254-256.*

9 - CROCE E., GOLIA M., AZZOLA M., RUSSO R., CROZZOLI L., OLSIN S., POMPA C., BORZIO M. : Laparoscopic choledochotomy with primary closure : *Surg. Endosc., 1996, 10, 1064-1068.*

10 - ROBINSON G., HOLLINSHEAD J., FALK G., MOULTON J. : Technique and results of laparoscopic choledochotomy for the management of bile duct calculi : *Aust. N.Z. J. Surg., 1995, 65, 347-349.*

11 - RHODES M., NATHANSON L., O'ROURKE N., FIELDING G. : Laparoscopic exploration of the common bile duct : lessons learned from 129 consecutive cases : *Br. J. Surg., 1995, 82, 666-668.*

12 - STOKER M. : Common bile duct exploration in the era of laparoscopic surgery : *Arch. Surg., 1995, 130, 265-269.*

13 - COX M., WILSON T., TOULI J. : Perioperative endoscopic sphincterotomy during laparoscopic cholecystectomy for choledocholithiasis : *Br. J. Surg., 1995, 82, 257-259.*

Surgical Laparoscopy & Endoscopy
Vol. 6, No. 6, pp. 421–423

Complications of Laparoscopic Fundoplication: The First 100 Patients

W. Munro, M.B.B.S., F.R.A.C.S., R. Brancatisano, M.B.B.S., F.R.A.C.S., I. P. Adams, B.Sc., and G. L. Falk, M.B.B.S., F.R.A.C.S.

Summary: Laparoscopic fundoplication is being performed with increasing frequency. The learning curve for the operation is long, and we herein discuss some of the problems we have experienced with this surgery. We also discuss changes we have made in our technique as the result of our experiences. **Key Words:** Laparoscopic fundoplication—Complications.

Laparoscopic fundoplication is being performed with increasing frequency (1,2) and the senior author (G.L.F.) has a relatively large experience with this procedure. The learning curve for the operation is long, and we herein communicate some of the problems we have experienced in the hope that this will prevent their repetition. We also discuss changes we have made in our technique as a result of our experience (3).

PATIENTS AND METHODS

From November 1991 to November 1993, the senior author performed laparoscopic fundoplications in 100 patients. The mean age was 49 years (range, 14–75). Fifty-eight patients were men and 42 women. Indications for surgery were standard: failure of proton pump inhibitor, drug dependence, or paraesophageal herniation. Patients all underwent preoperative endoscopy, biopsy, manometry, and 24-h pH study as minimum investigations. Barium swallow and biliary ultrasound were performed as indicated. Laparoscopy was attempted in the first 50 cases. The technique was a short floppy "Rosetti"-type fundoplication with full short gastric division (4). Criteria for immediate open operations in the second 50 patients were adhesions, previous gastric surgery, short esophagus, obesity, and gastric volvulus.

Received March 29, 1995; revision received August 18, 1995; accepted September 19, 1995.

From the Division of Upper Gastro-intestinal Surgery, Concord Hospital, Sydney, New South Wales, Australia.

Address correspondence and reprint requests to Dr. G. L. Falk, PO Box 1085, Strathfield NSW 2135, Sydney, New South Wales, Australia.

RESULTS

Fundoplication was completed in 89 patients by laparoscopy. Eleven patients required conversion at the first operation to completion by laparotomy.

COMPLICATIONS

Wrap migration

The complication of transdiaphragmatic migration of the fundoplication occurred in seven patients. Two patterns of presentation emerged: acute and delayed.

Acute

Two days postoperatively one patient suffered sudden onset of retching followed by epigastric pain radiating to the left chest. A barium study was performed which demonstrated gastric volvulus, and urgent repair was undertaken. The other patient retched in the recovery ward and developed similar chest pain 48 h after surgery. Barium study demonstrated an intrathoracic gastric volvulus and the pa-

tient was immediately returned to surgery. Postoperative recovery was prolonged.

Delayed

Five patients suffered a clinical syndrome of epigastric pain, early satiety, dysphagia, and nausea some time after surgery. The clinical symptoms were strikingly consistent and the pain radiated into the left chest. Diagnosis was by barium meal in all patients. The recurrent herniation followed initial laparoscopic repair, and reoperation was performed by laparoscopy in two patients and laparotomy in three. Four patients in this group had a history of vigorous retching in the recovery ward and had not been managed postoperatively with nasogastric tube section. Four patients also had no crural suturing performed as the hiatus had been judged small.

Dysphagia

The short gastric arteries were not generously divided in the first 15 patients, and five patients in this group suffered significant dysphagia requiring dilatation. Following dilatation, four patients had a good result, and one underwent reoperation and conversion to a partial wrap. This patient had dysphagia and a motility disorder that was misinterpreted on preoperative manometry; subsequently, the patient was found to have an amotile esophagus. In recognition of these results, the technique was modified to include generous division of the short gastric vessels and the posterior gastric vessels and short floppy fundoplication. Since then, no significant dysphagia has been encountered.

Visceral laceration

Visceral laceration occurred in two patients. The first case was early in the experience during a difficult dissection of a paraesophageal hernial sac. The anterior esophagus was punctured with a 5-mm grasper. Laparotomy and repair were performed.

A second patient suffered a perforation of the gastric fundus due to handling with graspers. This was recognized at the time and managed by immediate closure with an endoscopic linear stapling device. This second case was related to inexperience and use of a small grasper on the stomach. Subsequently, a softer bowel-handling instrument has been used to retract the stomach (Stortz–Dorsey clamp).

Conversion to laparotomy

Laparotomy was performed in 11 patients in this series after laparoscopic fundoplication was begun. Paraesophageal herniation, obesity, and previous upper abdominal surgery led to failure of the laparoscopic technique (Table 1).

Pulmonary embolism occurred in two patients who underwent conversion to laparotomy despite use of subcutaneous heparin, T.E.D. antiembolism (Kendan) stockings, and sequential compression devices. Wound dehiscence (n = 11), wound infection (n = 3), and spinal osteomyelitis secondary to an infected i.v. cannula site also occurred following conversion to laparotomy. Patients undergoing conversion after failed laparoscopy had a major complication rate of 6 of 11 (>50%).

The rate of conversion fell considerably as experience increased. After 50 cases had been performed, patients were preselected for open or laparoscopic fundoplication and the conversion rate decreased further (Table 1).

Complication rate

The rate of complications fell with experience, and a satisfactory level was only achieved after 50 cases (Table 2).

DISCUSSION

We have identified several technical problems associated particularly with laparoscopy for fundoplication. Laparoscopic judgment of the size of the hiatus is not possible unless the hiatus is calibrated with a bougie. We believe hiatal closure is mandatory to prevent migration. However, it must not be closed too firmly or dysphagia will result. We believe that leaving the hiatus unsutured contributed to wrap migration in four patients and to one episode of gastric volvulus in our series. Retching in the early postoperative period may predispose to failure of the procedure. Recurrent herniation did not develop in the large hiatal defects associated with paraesophageal herniation following suture approximation of the posterior crura.

Acute gastric volvulus after surgery was the most

TABLE 1. *Causes of conversion to laparotomy in laparoscopic fundoplication*

Pathology	No. of events	Case no.
Paraesophageal hernia	6	1, 5, 7, 11, 29, 46
Adhesions	3	1, 9, 29
Obesity	2	24, 71
Hypertrophy left lobe	1	28
Instrumental visceral injury	1	7
Short esophagus	1	11

TABLE 2. *Effect of experience on complication rates*

Case no.	Immediate complications	Late complications
1–10	4	1
11–20	3	4
21–30	3	0
31–40	1	3
41–50	2	0
51–60	0	1
61–70	2	2
71–80	0	0
81–90	0	0
91–100	0	0

dangerous complication encountered. The two patients both had violent retching in the recovery room without a nasogastric tube in place, and in retrospect we believe that volvulus in the chest occurred at that time. Diagnosis was difficult in the early postoperative period; volvulus was associated with a left pleural rub, left subcostal and back pain, and the inability to take fluids. Chest radiograph did not show an abnormality until day 3 in each case. Barium swallow is the best diagnostic investigation, and early diagnosis depends on clinical suspicion in the postoperative patient. Unexplained, severe, left-sided chest pain points to recurrent herniation and gastric volvulus. Hiatal closure and wrap fixation to the diaphragm and placement of a nasogastric tube for 24 h appeared to eradicate this complication in the later part of the series.

Other series recognizing the complication of volvulus have recommended similar technical procedures to prevent such occurrences (4,5). We now routinely administer ondansetron as an antiemetic intraoperatively and avoid narcotics in almost all patients. It is possible that some late recurrences in the era of open fundoplication actually occurred early by the mechanism of postoperative retching but were disguised by perioperative narcotic administration.

The early patients in our series had more dysphagia and bloat than the later group; in the later group, a more generous fundal mobilization was undertaken and tension on the wrap was reduced. With adequate mobilization the wrap lies behind the esophagus with no need to maintain the position by traction with forceps. Satisfactory postsurgical symptomatic outcome is achieved by adherence to the principles of short floppy fundoplication (6,7).

CONCLUSIONS

Our best results in terms of complications, conversion rates, and symptomatic outcome occurred in the second 50 cases. In these cases, we focused on calibration and suture of the hiatus in all patients; fashioning a short floppy fundoplication by short gastric division; control of postoperative retching by ondansetron and avoidance of narcotics; and selection of appropriate cases for laparoscopic repair. There is a considerable learning curve, and the best results will be obtained by surgeons with special interest and extensive experience in laparoscopic fundoplication.

Acknowledgment: To my long-suffering secretaries, Barbara and Sue, my eternal gratitude.

REFERENCES

1. Dallemagne B, Weerts JM, Jehaes C, Markiewicz S, Lombard R. Laparoscopic Nissen fundoplication: preliminary report. *Surg Endosc* 1991;1:138–43.
2. Falk GL, Brancatisano RP, Hollinshead J, Moulton J. Laparoscopic fundoplication: a preliminary report of the technique and post operative care. *Aust N Z J Surg* 1992;62:969–72.
3. Falk GL, Brancatisano RP. Fundoplicature laparoscopique: a propos d'une experience personnelle: 88 cas. *J Celio Chir* 1995;13:63–7.
4. Rosetti M, Hell K. Fundoplication for the treatment of gastroesophageal reflux in hiatal hernia. *World J Surg* 1977;1: 439–44.
5. Festen C. Paraoesophageal hernia: a major complication of Nissen's fundoplication. *J Pediatr Surg* 1981;16:496–9.
6. Turell WP, Smith EI, Carson JA. Gastroesophageal reflux in childhood. *Ann Surg* 1983;197:560–5.
7. DeMeester TR, Bonavina L, Albertucci M. Nissen fundoplication for gastro-oesophageal reflux disease. Evaluation of primary repair in 100 consecutive patients. *Ann Surg* 1986; 204:9–20.

Surg Endosc (1998) 12: 73–75

Surgical Endoscopy

Laparoscopically assisted massive splenectomy

A preliminary report of the technique of early hilar devascularization

I. A. Nicholson, G. L. Falk, S. C. Mulligan

Department of Surgery and Haematology, Repatriation General Hospital, Hospital Road Concord, Sydney, New South Wales, 2137 Australia

Received: 27 December 1996/Accepted: 19 February 1997

Abstract. Laparoscopic splenectomy has been safely performed for small spleens, but technical limitations have prevented massive splenectomy. We describe a technique of early hilar devascularization to enable massive splenectomy in three patients over the age of 80 years. Massive splenectomy was performed with minimal blood loss and minor morbidity. Early laparoscopic control of the splenic artery and vein will enable the safe removal of the massive spleen, without major laparotomy. Morbidity of splenectomy may be reduced by laparoscopy.

Key words: Massive splenectomy — Early hilar devascularization — Spleen

Splenectomy in the case of massive splenic enlargement has been an operation with a reported operative mortality of 20% and morbidity of 39% [1]—most apparent in the elderly population. Complications are hemorrhage, infection, and respiratory [1, 4, 5, 7]. The incision is of larger magnitude than that for open cholecystectomy, so laparoscopic splenectomy may offer many of the same advantages as laparoscopic cholecystectomy, including decreased respiratory complication and infection.

There have been multiple reports demonstrating the feasibility of laparoscopic splenectomy, predominantly in patients with normal-sized spleens [2, 3, 8, 9].

We report a technique used in three patients who underwent removal of massively enlarged spleens assisted by laparoscopy (Table 1).

Correspondence to: G. L. Falk, Post Office Box 1085, Strathfield NSW 2135, Australia

Technique

The patient is positioned with a sandbag under the left pelvis and left shoulder. The table is rolled approximately 30°. Ports are placed as displayed in Fig. 1. Three 10-mm ports and one 5-mm port are used to allow repositioning of the camera for visualization of the hilum (port 1) and also the lower pole (port 3). Division of short gastric vessels is performed first with endoclips to expose the splenic hilum (Fig. 2). The greater curve can then be retracted to the right. The splenic flexure of the colon is then mobilized to give access to the lower pole of the spleen. The hilum of the spleen is then displayed by moving the camera to port 1, and the splenic artery and vein are isolated over a 2–3-cm segment to give proximal control of the splenic artery before division with an endostapler (Fig. 3). A platelet transfusion is given now if necessary.

The artery and vein are divided using a vascular stapler and then suture ligated, keeping a laparoscopic clamp initially on splenic artery inflow in case of stapler misfire. Dissection is then completed by separating the hilum of the spleen from the tail of the pancreas under excellent vision. Division of the lienorenal ligament is the last maneuver. This is commenced inferiorly and a fan retractor is used to elevate the spleen. The telescope is placed in an inferior port to facilitate vision.

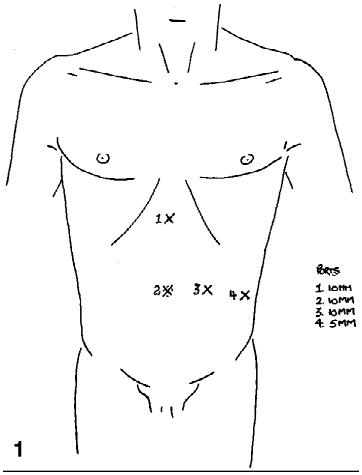
The spleen may be placed in a bag and removed piecemeal or be removed whole after a minimal iliac-fossa-type incision in the lower abdomen, dependent upon histopathological requirements.

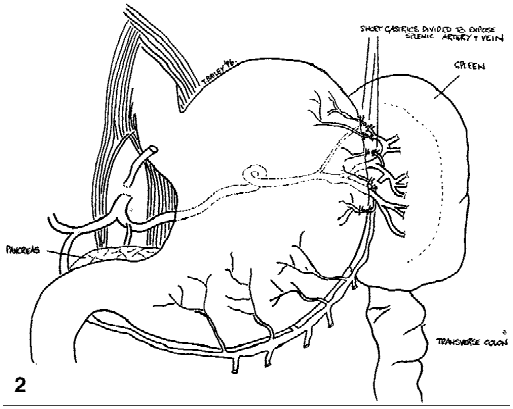
Results

The three patients underwent successful laparoscopic assisted massive splenectomy with minimal blood loss. Transfusion of 1 unit packed cells required for Hb < eight in one patient with pre-op anemia. There were no complications. There was no mortality. Length of stay varied between 4 and 7 days.

Discussion

Open splenectomy in patients with hematological disorders had a high morbidity and mortality [1] and would be considered by most to be significantly higher in a group of patients greater than 80 years. A significant proportion, 25% of postop complications, can be attributable to respiratory compromise and wound infections [5, 7]. This preliminary experience is encouraging in a group of patients most likely to develop respiratory complications from open surgery.





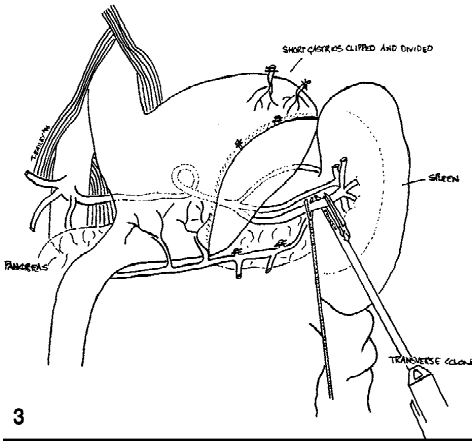


Fig. 1. Port placement for laparoscopic splenectomy.

Fig. 2. Division of short gastric vessels to expose splenic artery and vein.

Fig. 3. Division of splenic artery (followed by splenic vein).

Table 1. Patient data

Patient	Age	Indication	Diagnosis	Other illness[a]
1	81 F	Thrombocytopenia	NHL	
2	80 M	Thrombocytopenia	NHL	IHD, CAL, Anemia
3	80 F	Refractory CLL	CLL	IHD, SpDXRT

[a] SpDXRT, Splenic radiotherapy; NHL, non-Hodgkins lymphoma; CCL, chronic lymphatic leukemia; IHD, ischemic heart disease; CAL, chronic airway limitation. All of these patients had been considered marginal for laparotomy and splenectomy

Table 2. Outcome data

Patient	Operation time	Blood loss	Days bed	Hospital stay	Spleen wt.	Histology
1	190 min	20 ml	1	4	1,500 g	Monocytoid BNHL
2	170 min	200 ml	1	4	835 g	Follicular NHL
3	200 min	400 ml	3	7	1,980 g	CLL

BNHL, B cell non-Hodgkins lymphoma

The technique we describe is different than that described for idiopathic thrombocytopenic purpura (ITP) spleens [2, 3, 6, 8, 9] where splenic mobilization has been performed first. Early isolation of the major blood supply allowed removal of massively enlarged spleens with minimal blood loss, average 200 ml, and exposure of the major vessels was not technically challenging. The use of preoperative splenic embolization has been reported but does not appear necessary if splenic blood supply is controlled early [2].

The technique also allows for full histology of the spleen, which can be divided in a bag or removed en bloc through a muscle-splitting incision in the left lower abdomen.

No respiratory complications were seen, which parallels our experience with laparoscopic cholecystectomy. It is likely that the absence of an upper abdominal wound and no retraction on the lower rib cage plus the early mobilization of the patient with minimal analgesic requirements is largely responsible for this outcome.

The laparoscopic assisted technique described allowed for early recovery and minimal hospital stay (an average of 5 days) in an unfit elderly group of patients.

Conclusion

This preliminary experience indicates that laparoscopic assisted surgery for massive spleens may be a well tolerated

alternative to open splenectomy for elderly and high-risk patients. The procedure has not entailed major blood loss as yet and provided ample material for histological evaluation and diagnosis. This technique may have the advantage of rapid recovery, minimal hospital stay, and a significant reduction in morbidity and mortality.

We believe the technique of early hilar devascularization is the key to safe bloodless dissection of the massive spleen. This early experience is encouraging.

Acknowledgment. The authors wish to thank Mr. Troy Bailey for provision of the line drawings.

References

1. Danforth DN Jr, Fraker DL (1991) Splenectomy for the massively enlarged spleen. Am Surg 57: 108–113
2. Gigot JF, Healy ML, Ferrant A (1994) Laparoscopic splenectomy for idiopathic thrombocytopenic purpura. Fr J Surg 81: 1171–1172
3. Hashizume M, Sugimachi K, Kitano S (1994) Laparoscopic splenectomy. Am J Surg 167: 611–614
4. Hoefer PA, Scullin DC Jr, Silver LF (1991) Splenectomy for haematologic disorders: a 20 year experience. J Ky Med Assoc 89(9): 446–449
5. Jacobs P, Wood L, Dent DM (1992) Splenectomy in the myeloproliferative syndromes. A retrospective risk-versus-benefit analysis. South Afr Med J 81: 499–506
6. Liew SC, Storey DW (1995) Laparoscopic splenectomy. Aust NZJ Surg 65: 743–745
7. Neal TF Jr, Tefferi A, Witzig TE (1992) Splenectomy in advanced chronic lymphocytic leukaemia: a single institution experience with 50 patients. Am J Med 93(4): 435–440
8. Poulin EC, Thibault C (1993) The anatomic basis for laparoscopic splenectomy. Can J Surg 36(5): 484–488
9. Schlinkert RT, Braich T (1994) Laparoscopic assisted splenectomy for treatment of presumed immune thrombocytopenic purpura. Mayo Clin Proc 69: 422–424

FUNDOPLICATURE LAPAROSCOPIQUE
A propos d'une expérience personnelle : 88 cas

R. Brancatisano, G.L. Falk

Sidney - Australie

La chirurgie laparoscopique a rapidement évolué depuis que Philippe Mouret a décrit la première cholécystectomie laparoscopique en 1985 (1) et est maintenant entrée dans la pratique chirurgicale quotidienne. Plusieurs études ont montré la diminution de la morbidité et de la durée d'hospitalisation du fait de la chirurgie laparoscopique (2, 3, 4). La chirurgie laparoscopique antireflux pour les patients présentant un reflux gastro-œsophagien est en plein essor.
En 1991 Dallemagne présentait une première série de fundoplicatures laparoscopiques (5). En ce qui nous concerne, nous avons précédemment rapporté notre technique de fundoplicature laparoscopique et nos résultats préliminaires (6). Ces résultats mettaient en évidence le fait que ces bénéfices de la chirurgie laparoscopique, à savoir la réduction du séjour hospitalier, celle des douleurs postopératoires et le retour plus rapide à une activité normale, pouvaient être obtenus dans ce groupe de patients.
Nous décrivons ici la série personnelle de l'auteur principal (G.L.F.) qui comprend 88 patients opérés de façon consécutive par fundoplicature laparoscopique pour reflux gastro-œsophagien.

❒ PATIENTS ET MÉTHODE

Une étude prospective des patients successifs soumis à une fundoplicature laparoscopique a été entreprise à partir de 1992, lorsque fut réalisé le premier cas. Toutes les données ont été mises sur fiche pour pouvoir être incluses dans un programme informatique.

Tous les patients ont eu une endoscopie préopératoire par le chirurgien qui réalisa l'intervention. Le score de l'œsophagite a été évalué du grade I au grade IV. Des biopsies multiples ont été réalisées en cas de suspicion d'œsophage de Barret.

On ne pratiqua une PH métrie de 24 heures que dans les cas où le diagnostic était incertain ; tous les patients ont eu une manométrie œsophagienne.

Les 50 premiers patients ont tous été l'objet d'une tentative laparoscopique. Après l'expérience de ces 50 premiers cas, les patients suivants étaient sélectionnés soit pour la technique traditionnelle, soit pour une procédure laparoscopique selon le statut préopératoire.

Une étude détaillée des symptômes présentés par les 30 premiers patients opérés était effectuée par un médecin résidant qui n'avait pas participé à leur thérapeutique.

Vingt patients ont eu une endoscopie de contrôle postopératoire.

❒ TECHNIQUE

Notre technique initiale a été décrite précédemment (6).

Nous pensons que les principes les plus importants pour obtenir un excellent résultat sont :

- une réalisation laparoscopique identique à l'intervention par laparotomie,

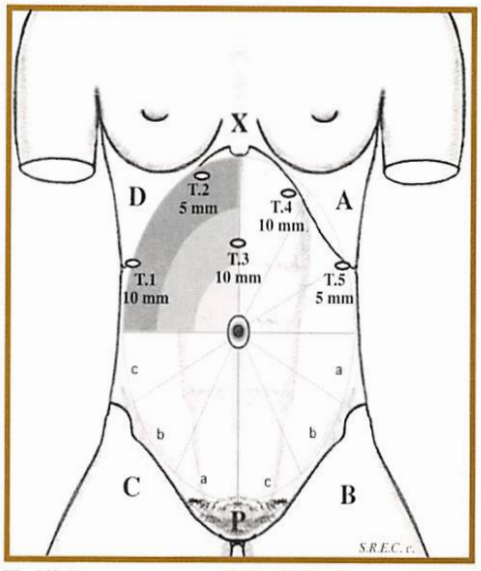


Fig N° 1 *Voies d'abord*

- une libération adéquate des vaisseaux courts de l'estomac,
- une fermeture de l' hiatus,
- le calibrage de la valve par une bougie de 50-60 French

Le patient est installé sur des jambières et la table d'opération est mise en proclive. Les trocarts sont placés comme il est indiqué sur la figure 1

L'essentiel de la dissection est effectué par l'intermédiaire des deux trocarts sous-costaux T2 et T4.

L'écartement du foie (T1), l'endoscope (T3), la dissection des vaisseaux courts est facilitée par l'utilisation des trocarts T2 et T3 pour les instruments de dissection utilisés par le chirurgien et par le télescope introduit par le trocart.

Résultats

La fundoplicature laparoscopique a été entreprise chez 88 patients ; l'âge moyen était de 50 ans, avec des extrêmes de 18 et 75 ans ; il y avait dans la série 51 hommes et 37 femmes.

Indications chirurgicales

Les indications pour cette fundoplicature laparoscopique étaient un reflux gastro-œsophagien résistant au traitement médical chez 66 patients, des phénomènes de régurgitation pulmonaire chez 8 patients, une sténose œsophagienne chez 5 patients et une hernie para-œsophagienne dans 11 cas.

Courbe d'apprentissage et taux de conversion	
Nombre de cas	**Nombre de conversions**
0 - 10	4
10 - 20	1
20 - 30	3
30 - 40	1
40 - 50	1
50 - 60	0
60 - 70	0
70 - 80	0
80 - 88	1

Tableau N° 2

Conversions en laparotomie N = 11	
Cause	**Nombre**
Hernie para-œsophagienne	6
Brachy-œsophage	1
Adhérences postopératoires	3
Antécédents de vagotomie HS	1
Obésité	2
Hypertrophie du lobe hépatique gauche	1
Perforation œso-gastrique	1

Tableau N° 1

Conversion de la fundoplicature en laparotomie

La chirurgie laparoscopique était tentée chez 88 patients. La conversion fut nécessaire dans 11 cas (Tableau 1). La majorité (8 patients) des conversions est survenue au cours des 30 premières interventions réalisées par laparoscopie.

Suites postopératoires précoces

La durée moyenne d'intervention a été de 150 minutes (extrêmes de 60 à 240 minutes) et la durée moyenne de séjour hospitalier postopératoire de 48 heures (extrêmes : 44 heures, 24 jours).

Nous n'avons pas utilisé de sonde naso-gastrique au cours des 50 premiers cas. Cependant, après avoir revu les premiers patients opérés, nous laissons en place systématiquement une sonde naso-gastrique pour les 24 premières heures postopératoires. Nous donnons ensuite aux patients des liquides, par petites quantités augmentant progressivement, cela de la 24ème à la 48ème heure et les patients quittent le service 48 heures après l'intervention, avec un régime liquide, mais sans restrictions.

Complications peropératoires

• *Une plaie viscérale* est survenue chez 2 patients :

- un patient avec une hernie para-œsophagienne a été l'objet d'une *plaie punctiforme de l'œsophage* pendant l'ablation du sac herniaire. Cette plaie a été suturée par chirurgie ouverte.
- *une plaie du fundus gastrique* se produisit au cours de la libération des vaisseaux courts chez un autre patient. Cette réparation du fundus a été réalisée à l'aide d'une agrafeuse endoscopique. Nous pensons que la perforation a été causée par l'utilisation d'instruments trop fins et agressifs et nous utilisons maintenant de façon routinière des clamps intestinaux conçus pour une préhension atraumatique (clamp laparoscopique "Dorsey", Stortz Co).

• *Un pneumothorax* est survenu chez deux patients : chaque fois une brèche avait été faite dans la plèvre gauche par la pince venant derrière l'œsophage et passant de droite à gauche (Fig N° 2). Les deux cas furent traités par drainage pleural, ce qui ne retarda pas leur sortie.

• *L'emphysème médiastinal* était présent chez 50 % des patients, à un degré variable, et jusque là n'a pas posé de problèmes. Nous ne pensons pas que l'emphysème médiastinal puisse être à l'origine d'un pneumothorax.

• *Un infarctus mineur de la rate* a été observé au pôle supérieur de celle-ci chez 5 patients, cela dans le contexte d'adhérences serrées entre l'estomac et la rate. L'infarctus est évident en cours d'intervention et se traduit dans les suites par une vidange gastrique retardée, une douleur scapulaire gauche et une sensibilité de l'hypocondre gauche. La splénectomie n'a été nécessaire chez aucun de ces patients.

INCIDENTS PEROPERATOIRES		
Complications	**Nombre de patients**	**N° cas**
Saignement sur site de trocart	1	29
Infarctus du pôle supérieur de la rate	5	37, 58, 67, 72, 74
Plaie viscérale	2	7, 39
Pneumothorax	2	5, 20

Tableau N° 3

La durée d'hospitalisation a été prolongée jusqu'au 7ème ou 10ème jour postopératoire pour pouvoir effectuer une analgésie et une alimentation parentérale. Nous pensons que ces infarctus ont pour cause la ligature de la branche verticale d'une artère en forme de T qui participe à la vascularisation à la fois de l'estomac et du pôle supérieur de la rate, et que cet accident devrait être évité par une dissection restant au contact de l'estomac.

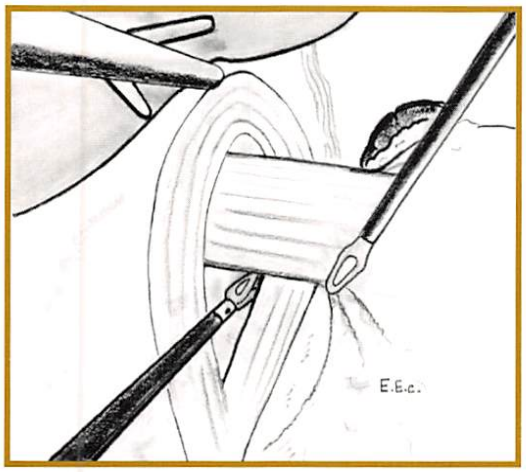


Fig N° 2 *Cause du pneumothorax*

Complications postopératoires précoces

Un volvulus gastrique aigu survint après de violents efforts de vomissements postopératoires en salle de réveil chez 2 patients. Ces 2 patients durent subir une chirurgie ouverte pour réduire la hernie. Aucun des deux n'avait de sonde naso-gastrique en postopératoire précoce (Tableau 4).

COMPLICATIONS POSTOPÉRATOIRES IMMÉDIATES	
Embolie pulmonaire	2 **
Hernie sur site de trocart	1 *
Infection de paroi	3 ***
Atélectasie basale	7 ****
Crise asthmatique	1
Volvulus gastrique	2
Hémorragie ulcéreuse duodénale *(Toradol)*	1
** nombre de conversions en laparotomie*	

Tableau N° 4

Complications tardives

Nous avons observé *une ascension tardive de la valve* chez 5 patients ; tous avaient présenté des efforts de régurgitation violents dans la période postopératoire précoce. Un tableau clinique fait de douleurs épigastriques et de l'hypocondre gauche, satiété précoce, dysphagie et nausées, est hautement évocateur d'étranglement de la fundoplicature dans l'hiatus. Le diagnostic put être réalisé par un transit baryté dans tous les cas.

Deux patients ont été repris par laparoscopie et trois par laparotomie (Tableau 5).

COMPLICATIONS TARDIVES	
Éventration postopératoire	1 *
Ascension de la valve	5
Dysphagie persistante	2
**laparotomie de conversion*	

Tableau N° 5

Réinterventions

Neuf patients nécessitèrent une réintervention après fundoplicature laparoscopique. Les causes de ces réinterventions sont présentées dans le tableau 6. L'ascension de la valve en fut la première cause.

RÉINTERVENTION APRES FUNDOPLICATURE LAPAROSCOPIQUE		
	Nombre de patients	**N° des cas**
Volvulus gastrique	2	25, 42
Ascencion de la valve	5	18, 40, 31, 64, 73
Dysphagie persistante	2	4,13
Hémorragie ulcéreuse	1	68
Total	**10**	

Tableau N° 6

Résultats fonctionnels

Nous avons pu effectuer une appréciation clinique détaillée des 88 premiers patients. Trois des patients ne purent être contactés pour cette étude. La période de suivi s'étend de 4 à 52 semaines, avec une moyenne de 28 semaines.

Le contrôle de la symptomatologie de reflux a été obtenu chez 88 patients.

La dysphagie a été un problème majeur dans 2 cas et transitoire dans 8. Ces 8 cas de dysphagie transitoire correspondaient à des patients opérés au début de la série,

quand une libération minimale des vaisseaux courts était réalisée. Des dilatations endoscopiques furent réalisées chez ces 8 patients avec un très bon résultat (tableau 7). La dysphagie a persisté dans 2 cas et ces 2 patients ont dû subir une réintervention avec, comme résultat, une amélioration partielle de leurs symptômes. Un patient présente une dysphagie persistante, liée à des troubles moteurs de l'œsophage.

Un contrôle endoscopique a été effectué chez 20 patients. Il n'y avait pas de cas de récidive de l'œsophagite.

RÉSULTATS FONCTIONNELS	
Contrôle de la symptomatologie de reflux	26 (96,6%)
Gas bloat transitoire	5
Possibilité d'éructation	19
Dysphagie persistante	2
Dysphagie transitoire	8
Confort digestif :	
- 100 %	24
- 80 %	1
Échec	2

Tableau N° 7

❒ DISCUSSION

Un reflux gastro-œsophagien sévère est une maladie de toute une vie. Une rechute des symptômes et de l'œsophagite est inévitable après arrêt du traitement médical (7). La chirurgie antireflux conventionnelle ouverte était jusqu'à ce jour la seule possibilité de traitement définitif et il avait été démontré qu'elle était supérieure au traitement médical avec les anti HZ dans la seule étude randomisée importante réalisée (8).

Depuis peu est apparue la fundoplicature laparoscopique ; elle offre aux patients la possibilité d'un contrôle du reflux à long terme avec une morbidité minime. Le taux de conversions que nous présentons dans notre série est le reflet d'un taux de complications peropératoires difficilement acceptable. A l'origine de ces conversions, on peut retenir 2 facteurs : d'une part l'expérience chirurgicale en procédures laparoscopiques, d'autre part les facteurs propres aux patients.

Au début de notre expérience, les hernies para-œsophagiennes ont nécessité des conversions mais, actuellement, nous réalisons de façon régulière, sans incident, des fundoplicatures laparoscopiques pour les hernies para-œsophagiennes .

Nous réfutons actuellement d'autres patients pour la fundoplicature laparoscopique, en particulier ceux qui ont des antécédents de chirurgie gastrique, de chirurgie hiatale ou un brachy-œsophage.

Une approche sélective au cours des 38 derniers cas opérés a permis d'obtenir une diminution très importante du taux de complications peropératoires (Tableau 2).

L'ascension postopératoire de la valve de fundoplication, soit qu'elle vienne se coincer dans l'hiatus, soit qu'elle soit à l'origine d'un volvulus gastrique, a été un problème. Chez 5 des 7 patients présentant cette complication, celle-ci était associée à des efforts de régurgitation importants, habituellement en salle de réveil, ce qui est à l'origine d'une ascension de la fundoplicature dans le thorax, au travers d'un hiatus insuffisamment fermé. Il est bien admis actuellement que l'appréciation de la taille de l'hiatus en cours de laparoscopie est difficile, et nous effectuons systématiquement la suture de ce hiatus sur une bougie.

On peut ajouter à cela que le fait de n'avoir pas utilisé de façon systématique une sonde naso-gastrique au cours des premières heures postopératoires, dans les 50 premiers cas, a pu contribuer à ce problème. Ainsi, depuis que nous effectuons de façon systématique un calibrage et une suture de l'hiatus et que nous plaçons une sonde naso-gastrique durant les 24 premières heures postopératoires, nous n'avons plus rencontré ce type de problème.

En chirurgie ouverte, il a été démontré que c'étaient les valves assez courtes et peu serrées qui donnaient le moins d'inconvénients postopératoires de type dysphagie ou gas-bloat (9, 10).

Une opération telle que celle-la ne peut être effectuée qu'avec une libération assez étendue des vaisseaux courts de l'estomac. Cette libération des vaisseaux courts par voie laparoscopique représente la partie la plus difficile de l'intervention. Au début de notre expérience, nous ne réalisions qu'une libération insuffisante des vaisseaux courts, (ce qui fut le cas chez 15 patients). Cela fut à l'origine d'une dysphagie assez sévère et prolongée, nécessitant des dilatations endoscopiques chez 8 de ces 15 patients. Ce problème a pratiquement disparu lorsque nous avons fait régulièrement ensuite une libération plus étendue des vaisseaux courts.

❒ CONCLUSION

Le contrôle du reflux obtenu par fundoplicature laparoscopique est excellent.

La période d'apprentissage pour la procédure laparoscopique fut longue et pénible : les patients qui nécessitent une intervention chirurgicale pour le reflux ne sont pas très nombreux. Les meilleurs résultats dans notre expérience ont été obtenus après un temps d'apprentissage long.

Le bilan préopératoire de ces patients doit être complet, incluant une endoscopie et une manométrie chez tous et la possibilité de réaliser une étude PH métrique sur 24 heures dans le cas d'incertitude diagnostique.

Pour obtenir de bons résultats, avec une fundoplicature laparoscopique, nous recommandons les principes suivants :

1 - une libération adéquate des vaisseaux courts,
2 - une valve courte et lâche,
3 - une fermeture de l'hiatus sur sonde de calibrage,
4 - une fixation de la valve au pilier et au diaphragme,
5 - au minimum 24 heures de sonde naso-gastrique en postopératoire,
6 - un traitement précoce et adapté des nausées et efforts de vomissements postopératoires.

Concord Hospital - Department of Surgery
Sidney NSW - Australia

Correspondance :

G.L. Falk.
PO Box 1085
Strathfield NSW 2135 - Australia

Nous tenons à remercier le Professeur David Gillet pour son aide à réalisation de ce travail, nos fidèles secrétaires Barbara et Sue et les membres de l'équipe chirurgicale de l'Adventist Hospital, Strathfield Hospital et Concord Hospital à Sydney, où un énorme développement de mise au point fut établi.

RESUME

Nous examinons les résultats de 88 fundoplicatures par laparoscopie pour hernie hiatale, afin de mettre en évidence la meilleure technique pour éviter les complications et obtenir le meilleur résultat au niveau symptomatique. Nous conseillons le dissection des vaisseaux gastriques courts et la fermeture des piliers du diaphragme en arrière de l'œsophage. La fundoplicature et la fermeture diaphragmatique doivent être calibrées grâce à une bougie de 56-60 French afin d'assurer une dyspagie minimum.

SUMMARY

We review the results of 88 laparoscopic fundoplications for hiatal herniation with a view to establishing the best technique to avoid complications and best symptomatic outcome. We commend division of the short gastric vessels and crural closure posteriorly. The fundoplication and diaphragmatic closure must be "calibrated" with a 56-60 French bougie to ensure minimal dysphagia.

BIBLIOGRAPHIE

1 - MOURET Ph. : From the first laparoscopic cholecystectomy to the frontiers of laparoscopic surgery. : *The prospectiveve future 1991 Dig. Surg. 8 : 124.*
2 - THE SOUTHERN SURGEONS CLUB (1991).: A prospective analysis of 1518 laparoscopic cholecystectomies. : *N. Engl. J. M. 18, 1073-8.*
3 - BERCI G. & SACKIER J. (1991). : The Los Angeles experience with laparoscopic cholecystectomy.: *Am. J. Surg. 161, 385-7.*
4.- CUSCHERIi A., DUBOIS F., MOUIEL J. et at (1991) : The European experience with laparoscopic cholecystectomy. : *Am. J. Surg. 161, 385-7.*
5.- DALLEMAGNE B., WEERTS J.M., JEHAES C., et al (1991).: Laparosoopic Nissen Fundoplication. Preliminary report. : *Surg. Laparosc. Endosc. 1, 138-43.*
6.- FALK G.L., BRANCATISANO R.P., HOLLINSHEAD J., MOULTON J. (1992) : Laparoscopic Fundoplication : A preliminary report of technique and post operative course. : *Aust N Z J Surg 62, 969-972.*
7.- HETZELI D.J., DENT J., REED W.D., et al (1988). : Healing and relapse of severe peptic œsophagitis after treatment with Omeprazole. : *Gastroenterology 95, 903-12.*
8.- SPECHLER S.J., et al (1992). : Comparison of medical and surgical therapy for complicated gastro-œsophageal reflux disease in veterans. : *New Engl. J. of Med. 326 : 786-790.*
9.- BOMBECK C. T. (1977). : Invited commentary. : *World J. Surg. 4 :45-51.*
10.- DEMEESTER T.R., JOHNSON L. F., KENT A.H., (1974). : Evaluation of current operations for the prevention of gastro-œsophageal reflux. : Ann. Surg. *1980, 511-23.*

SURGICAL TECHNIQUE

Aust. N.Z. J. Surg. (1995) **65**, 347–349

TECHNIQUE AND RESULTS OF LAPAROSCOPIC CHOLEDOCHOTOMY FOR THE MANAGEMENT OF BILE DUCT CALCULI

G. ROBINSON, J. HOLLINSHEAD, G. FALK AND J. MOULTON

Department of Surgery, Concord Hospital, Concord, New South Wales, Australia

Laparoscopic choledochotomy has been performed in 50 patients to remove common bile duct calculi demonstrated on routine operative cholangiography at the time of laparoscopic cholecystectomy. The patients ranged from 16 to 91 years old. One patient died, giving a mortality of 2%. At postoperative T-tube cholangiography, retained stones were demonstrated in three patients (6%) with all stones being removed using a choledochoscope via the T-tube track. Laparoscopic common bile duct exploration via a choledochotomy is a feasible and effective method to manage common bile duct calculi demonstrated during laparoscopic cholecystectomy.

Key words: choledocholithiasis, choledochotomy, laparoscopy.

INTRODUCTION

Laparoscopic cholecystectomy is established as the treatment of choice for symptomatic gall-bladder calculi. The optimal method of management of bile duct calculi in patients undergoing laparoscopic cholecystectomy remains controversial. An ERCP and endoscopic extraction following sphincterotomy,[1] laparoscopic exploration techniques[2–4] and open bile duct surgery,[5] as performed prior to the introduction of laparoscopic cholecystectomy, remain the treatment options for the management of common bile duct (CMD) calculi.

Based on the premise that successful laparoscopic procedures are adaptations of established procedures performed at open surgery, a technique for bile duct exploration at the time of laparoscopic cholecystectomy has been developed. A choledochotomy is performed, the bile duct is explored using a flexible choledochoscope and a T-tube is sutured into the CBD in the standard manner using laparoscopic techniques. Our experience with 50 patients is presented.

METHODS

The operation can be performed readily either from the side of the patient (American approach) or by standing between the patient's legs (French approach). Operating ports are placed as for laparoscopic cholecystectomy except that a 10 mm instead of a 5 mm port is placed in the right subcostal position (Fig. 1, Port 3). This can be placed from the outset if bile duct calculi are suspected. The gall-bladder is retracted superiorly using a grasping forceps through the right lateral 5 mm port (Fig. 1, Port 2) and the cystic structures dissected and displayed.

Operative cholangiography is performed on a routine basis by placing a 3Fr round tip catheter with no side holes through a small incision in the cystic duct. The catheter is passed through a long, wide-bore needle in the Toohey needle configuration (Concord cholangiogram set, William A. Cook Australia Pty Ltd, Cat. No. 13911). The catheter is held in place with a metal clip closed on the cystic duct and catheter, firm enough to hold the catheter but not obstruct it. The cholangiogram is performed using an image intensifier that has the capability to take spot high quality films during the screening.

When calculi are demonstrated in the bile duct a decision is made as to the most effective method for removing them. The options include laparoscopic choledochotomy, transcystic exploration or exploration of the bile duct at laparotomy. Our current experience indicates that most patients can be explored using laparoscopic choledochotomy. The technique for the procedure will be described in detail.

Exposure was achieved by elevating the liver using the forceps on the fundus of the gall-bladder. In most cases the cystic duct was not divided. However, when the cystic duct limits the exposure of the bile duct, it is divided.

Analogous to open surgery, the duodenum is retracted inferiorly to expose the bile duct. This is achieved by placing a fifth port in the left upper quadrant just below the costal margin in the mid-clavicular line (Fig. 1, Port 5). An atraumatic bowel holding forceps or a fan retractor can be passed through this port to retract the duodenum and proximal transverse colon inferiorly. Visualization of the CBD can be further enhanced by the use of an angled (30°) telescope.

Frequently, the CBD can be seen through the loose areola tissue and is readily dissected. When the overlying tissues are thickened the CBD is located by dissecting down the cystic duct to the CBD. It is important at this stage to avoid dissecting the CBD along its inferoposterior surface.

The dissection is performed using a two-handed technique similar to that used when displaying the bile duct at open surgery. A dissecting forceps is passed through Port 3 (Fig. 1) to lift the tissues overlying the bile duct. The dissection is performed using either diathermy scissors or a dissecting hook passed through Port 4 (Fig. 1) to display 2–3 cm of bile duct. This allows for a wide choledochotomy which will facilitate easy access to the duct and subsequent placement of a T-tube. Using a two-handed dissection technique allows division of overlying tissue under tension and minimizes the risk of bile duct injury.

The choledochotomy can be performed using a specially

Correspondence: Mr J. Hollinshead, Department of Surgery (2FC), Concord Hospital, Concord 2139, New South Wales, Australia.

Accepted for publication 18 August 1994.

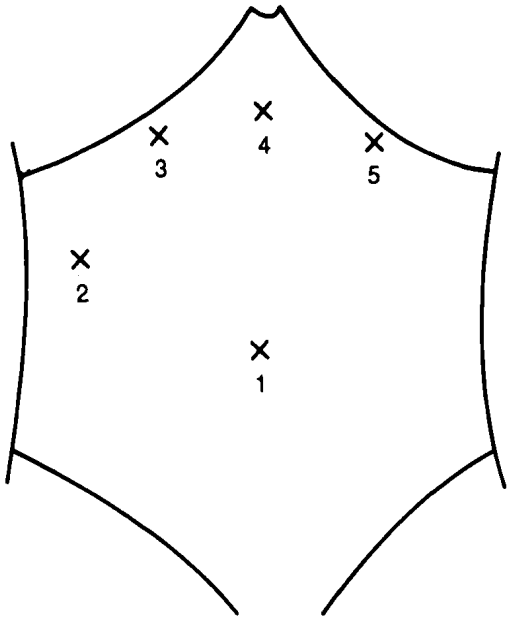


Fig. 1. Part placements.

constructed long-handled scalpel that can be passed through the midline 10 mm operating port. A Beever blade is fixed on to the end of the scalpel. Alternative techniques are to use a thin hook wire dissector with cutting diathermy or fine sharp pointed endoscissors. Once entry to the duct is obtained the choledochotomy can be readily extended longitudinally as required using sharp endoscissors.

On performing choledochotomy, stones are seen frequently at the opening or gush out with the bile. Obvious stones can be removed with fenestrated dissecting forceps and blunt forceps can be used to 'milk' stones both from above and from below into the choledochotomy for easy extraction.

Retrieval of residual stones can be accomplished using dormia baskets, stone grasping forceps, balloon catheters and irrigating catheters passed through a standard choledochoscope. The choledochoscope is introduced through either the right upper quadrant or midline 10 mm ports (Fig. 1, Ports 3 or 4). It is best introduced through the long Storz 5 mm reducing sleeve. This provides a stiffener which controls the flex of the scope in the peritoneal cavity and facilitates entry of the scope through the choledochotomy. Damage to the choledochoscope may result from handling it directly with endoforceps or passing it through a flap valve port and should be avoided.

Proximal and distal choledochoscopy is performed with saline irrigation. Excellent views of the bile duct are obtained by placing the saline flask approximately 1 m above the patient's abdomen. Video coupling is advantageous but direct vision is sufficient. Stone clearance of the biliary tree is confirmed and a T-tube of appropriate size inserted.

The T piece of the T-tube is trimmed in the same way as when performing open exploration and the exit limb is shortened to allow for ease of handling. The whole T-tube is then passed into the abdominal cavity via one of the 10 mm ports. The exit limb is placed up over the liver and the T limbs are manoeuvred by use of grasping forceps into the choledochotomy. The choledochotomy is closed using interrupted 3/0 absorbable sutures which are tied intracorporally.

The cystic duct and artery are divided and the gall-bladder removed. A closed suction drain is placed into the gall-bladder bed adjacent to the choledochotomy and brought out through the right lateral port (Fig. 1, Port 2). The T-tube is brought out through the right upper quadrant port (Fig. 1, Port 3). It has been our practice to rely on choledochoscopy to ensure duct clearance, however a completion cholangiogram can be performed once the T-tube has been exteriorized.

A T-tube cholangiogram is performed on day 4 following the operation, without prior clamping of the T-tube. Provided there is no residual stone, free flow of contrast into the duodenum and no obvious bile leak, the T-tube is clamped. If there is no pain or bile leakage after 12–24 h, the drain is removed and the patient discharged home with the T-tube *in situ*. The T-tube is removed on an outpatient basis 2 to 3 weeks postoperatively.

RESULTS

The first laparoscopic choledochotomy and bile duct exploration was performed in December 1991. Since then 52 laparoscopic bile duct explorations have been attempted. Conversion to open bile duct exploration was required in two patients, one because an aberrant right hepatic artery was anterior to the CBD making laparoscopic dissection hazardous and, in a second patient, gross inflammatory thickening prevented adequate demonstration of the CBD.

The patients' age range was 16 to 91 years (mean 56). There were 29 women and 21 men. A total of 12 patients had no clinical, biochemical or imaging criteria to suggest stones would be found in the CBD.

All patients underwent successful proximal and distal choledochoscopy. There were two negative explorations. The largest calculus removed measured 14 mm in diameter, while the greatest number of stones removed from any one duct was 19. Operating times ranged from 110 to 360 min (mean 216).

The procedure was undertaken by 11 different surgeons. Three surgeons have performed more than eight explorations while the remaining eight surgeons, four of whom were surgeons-in-training, have performed less than eight each. Of significance, surgeons-in-training have performed 12 explorations (24%). The more experienced surgeons are now taking 2½ to 3 h for the entire procedure of cholecystectomy and exploration of the bile duct.

The average postoperative stay has been 7 days (range 4–19). The T-tube was removed at a mean of 20 days postoperative (range 8–49).

Prolonged drainage from the gall-bladder bed drain occurred in five patients lasting from 2 to 4 days. All settled without further intervention. One T-tube was removed inadvertently on the 8th postoperative day and the patient developed a significant bile collection necessitating repeat laparoscopy and lavage of the bile. The laparoscopically placed drain to the bile duct controlled the leak and his subsequent recovery was uneventful.

All patients underwent T-tube cholangiography on the 4th postoperative day. Retained stones were demonstrated in three patients. The first patient had a 3 mm stone in an intrahepatic bile duct which after 5 weeks dropped into the CBD and was retrieved by percutaneous choledochoscopy via the T-tube tract. The other two patients had single retained

stones which were also retrieved using the choledochoscope via the T-tube tract 5 weeks postoperatively.

There were no displaced T-tubes, wound infection occurred in three patients but settled readily with drainage and dressings by the patient. There were no port site hernias, no visceral injuries, no deep venous thrombosis (DVT) and no septic complications. One patient had a pulmonary embolus and two had mild chest infections.

There was one death, a 91 year old frail, high-risk female patient who was admitted with an empyema of the gallbladder and signs of systemic toxicity which failed to resolve on conservative treatment. A decision was made to proceed with laparoscopic cholecystostomy. At operation there was a pericholecystic abscess in association with a gangrenous empyema resulting in disintegration of the fundus on attempting to place the cholecystostomy tube. Further dissection with a view to cholecystectomy was then undertaken. The cystic duct was identified and operative cholangiography revealed pus coming from the cystic duct and multiple stones in the CBD. The procedure was then extended to laparoscopic choledochotomy to remove the bile duct calculi and resolve the sepsis. The patient's condition was stable throughout the procedure. Three hours postoperatively, while still in the recovery ward, the patient developed an irreversible, lethal cardiac arrythmia.

DISCUSSION

The technique of laparoscopic choledochotomy enables the surgeon to deal with bile duct stones found at the time of laparoscopic cholecystectomy without having to proceed to open surgical exploration or having to rely on ERCP sphincterotomy and stone extraction. In order to perform the procedure surgeons have to develop the additional skills of laparoscopic suturing and percutaneous choledochoscopy.

Very little additional equipment is required, an important consideration in this era of ever increasing cost restraints. The only additional instruments required are needle holders and either a bowel-holding forceps or a fan retractor to retract the duodenum. Standard flexible choledochoscopes used in the pre-laparoscopic era are suitable for extraction of stones as well as confirmation of ductal clearance. There is no requirement to purchase small, more fragile laparoscopes advocated for attempted clearance of bile duct stones via the cystic duct.

When compared with the transcystic approach[2,4] to clear bile duct calculi at laparoscopic cholecystectomy this technique has the advantages of reliable access to the intrahepatic ducts and easy retrieval of large and multiple stones without the need to purchase further specialized equipment. Furthermore, the technique is a laparoscopic adaptation of an established open surgical technique with predictable complications and outcome.

The mean operating time of 3½h is prolonged. The prolonged operating time in part reflects the fact that the patients reported in this series represent the developmental phase of the procedure. The incidence of postoperative complication normally associated with prolonged anaesthesia such as DVT pulmonary emboli, cardiorespiratory complications and abdominal sepsis are acceptably low. The one patient who died had prolonged anaesthetic and remained stable throughout the procedure. Her death was considered to be more related to her underlying problem of being a frail, elderly lady with severe sepsis involving the biliary tree rather than the prolonged anaesthetic.

Patients undergoing laparoscopic bile duct exploration make a rapid postoperative recovery similar to that seen with laparoscopic cholecystectomy. Our mean postoperative stay of 7 days is excessive and does not reflect the potential for this procedure to reduce the hospital bed stay. This series of patients represents the developmental phase of the procedure during which time a cautious conservative approach was adopted; an approach we considered not to be unreasonable as many of our patients were elderly (34% over 70 years). In the future we envisage removal of the drain and discharging many of our patients on day 2 postoperatively with the T-tube on free drainage. A T-tube cholangiogram would then be performed on days 5 to 7 postoperatively as an outpatient procedure and provided there is no abnormality the T-tube would be clamped.

As there is minimal tissue disturbance when compared with open surgery and the concern that modern Silicone/latex T-tubes appear to be less reactive than their predecessors we have adopted a practice of delayed T-tube removal as an outpatient 2 to 3 weeks following surgery. The only T-tube related problem was a bile collection following the inadvertent premature removal of a T-tube 8 days postoperative which required re-operation. The T-tube causes minor patient discomfort and no other untoward problems have been encountered.

Although the majority of explorations have been performed by the two senior authors, the procedure in our institution has been taken up by all general surgeons and approximately one-quarter have been performed by surgeons-in-training. Our experience would indicate that, with appropriate training, surgeons performing laparoscopic biliary surgery on a regular basis can use this technique for the management of bile duct calculi found at the time of laparoscopic cholecystectomy.

REFERENCES

1.. Cotton PB. Endoscopic retrograde cholangiopancreatography and laparoscopic cholecystectomy. *Am. J. Surg.* 1993; **165**: 474–8.
2.. Fletcher DR. Common bile duct calculi at laparoscopic cholecystectomy: A technique for management. *Aust. N.Z. J. Surg.* 1993; **63**: 710–14.
3.. Phillips EH, Carroll BJ, Fallas MJ. Laparoscopically guided cholecystectomy: A detailed report of the first 453 cases performed by one surgical team. *Am. Surg.* 1993; **59**: 235–42.
4.. Petelen JB. Laparoscopic approach to common duct pathology. *Am. J. Surg.* 1993; **165**: 487–91
5.. Pitt HA. Role of open choledochotomy in the treatment of choledocholithiasis. *Am. J. Surg.* 1993; **165**: 487–91.

THE MANAGEMENT OF PERFORATION OF THE DUODENUM FOLLOWING ENDOSCOPIC SPHINCTEROTOMY: A PROPOSAL FOR SELECTIVE THERAPY

P. Y. SCARLETT AND G. L. FALK

Department of Surgery, Concord Hospital, Sydney, New South Wales, Australia

The successful non-surgical management of retroduodenal perforation following endoscopic sphincterotomy is reported and the literature reviewed. Two patients are described who developed gas in the retroperitoneum following endoscopic sphincterotomy. One patient developed retroperitoneal emphysema and cervical emphysema, while the second patient developed retroperitoneal emphysema and a pneumothorax following endoscopic sphincterotomy. Both patients were treated conservatively and made uneventful recoveries. An algorithm for assessment and treatment is proposed based on the authors' experience and a literature review. Patients with confirmed ongoing duodenal leakage, sepsis or collection should have expeditious surgery.

Key words: duodenal perforation, endoscopic sphincterotomy, therapy.

INTRODUCTION

Retroduodenal perforation of the duodenum is a well recognized complication of endoscopic sphincterotomy (ES) occurring in 1.1% of cases (Table 1). Most perforations occur posteriorly, behind the pancreatic head or uncinate process.[1] The risk of perforation increases with the length of sphincterotomy,[2] the presence of a short intramural segment of distal common bile duct, transampullary extraction of larger gallstones, the use of pre-cut sphincterotomy, repeated attempts at sphincterotomy,[3] and is inversely related to the diameter of the common bile duct.[4,5] The two reported cases represent the experience of perforation in 280 cases of ES.

Both patients had papillary stenosis and both required use of the pre-cut sphincterotome. The authors' experience in this regard confirmed the report of Sherman *et al.* who found that complications were more frequent when sphincterotomy was performed for sphincter of Oddi dysfunction.[5]

There have been widely differing views on the management of perforation of the duodenum following ES ranging from conservative treatment [4,6–8] to further endoscopic retrograde cholangiopancreatography (ERCP) with demonstration of the progress of contrast extravasation,[9] to the traditional surgical management of all perforations.[3,10,11] The place of surgery after initial failure of conservative therapy is also unclear with most authors resorting to surgery after patient deterioration or with the development of complications[4,12–14] and others persisting with non-operative treatment despite clinical deterioration.[15]

Patients requiring laparotomy for clinical deterioration as reported in the literature have a mortality rate approaching 50% (Table 1). This closely parallels the experience of perforation of the duodenum following blunt trauma, where delay in operative management is associated with a marked increase in mortality.[16] The

Table 1. Incidence of duodenal perforation in reported endoscopic series

Group	No. patients	No. perforations	No. operations	Deaths
Ponchon *et al.*[18]	19	1	1	—
Neoptolemos *et al.*[19]	144	0	—	—
Shemesh *et al.*[20]	44	0	—	—
Hansell *et al.*[6]	121	3	—	—
Ghazia and McSherry[7]	40	1	—	—
Escourrou *et al.*[21]	407	6	3	—
Neoptolemos *et al.*[10]	190	1	1	1
Cotton and Vallon[22]	679	5	1	1
Viceconte *et al.*[23]	296	0	—	—
Cotton[24]	134	0	—	—
Koch *et al.*[11]	267	2	—	—
Neuhaus and Safrany[4]	400	2	—	—
Safrany[8]	243	8	1	—
Vaira *et al.*[25]	1 000	5	1	—
Sarr *et al.*[12]	254	5	4	—
Booth *et al.*[3]	56	5	5	1
Leese *et al.*[17]	394	3	2	1
Dunham *et al.*[9]	820	8	2	2
Safrany[26]	3 618	40	19	14
Byrnes[15]	57	2	—	—
Geenen *et al.*[14]	1 250	14	9	2
Martin and Tweedle[27]	795	9	—	—
	11 228	120	49	22

Correspondence: Mr G. L. Falk, PO Box 1085, Strathfield, NSW 2135, Australia.

Accepted for publication 28 April 1994.

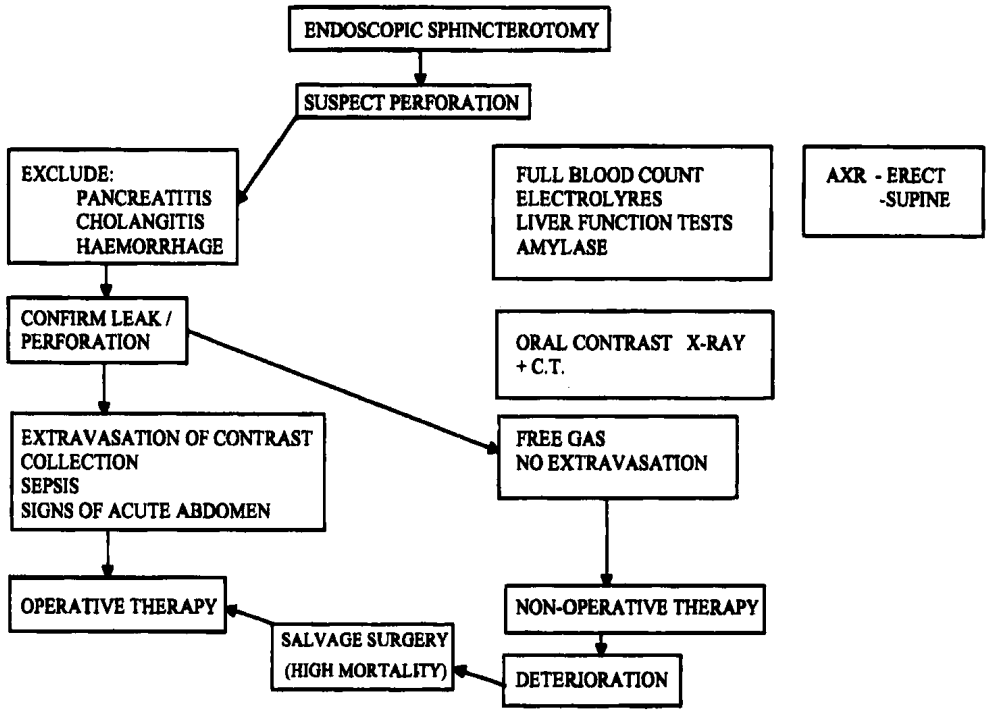


Fig. 1. Management algorithm.

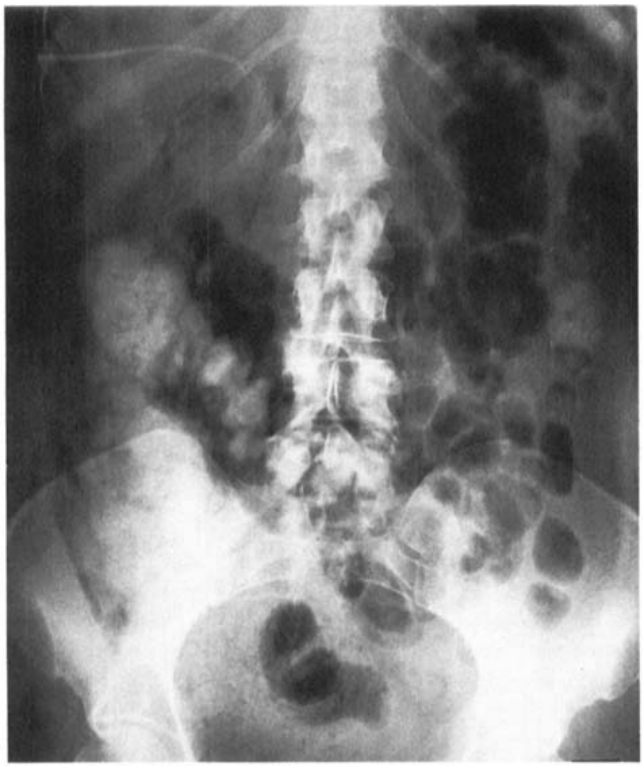


Fig. 2. Intraperitoneal and retroperitoneal gas following ERCP duodenal perforation.

deaths in the reported series of perforation following ES have occurred where surgical therapy has been delayed. No criteria for the selection of patients for conservative or immediate operative treatment have been proposed.

Two case reports are presented of patients having perforation of the duodenum following ES, who were treated successfully with conservative therapy, and a management algorithm is proposed for the selection of patients for conservative or operative therapy (Fig. 1).

Case 1

A 54 year old woman was admitted for endoscopic sphincterotomy for a suspected retained common bile duct stone, 9 years following cholecystectomy. She had been experiencing typical biliary pain, but had normal liver function tests. An ultrasound scan suggested the presence of a stone at the lower end of the common bile duct.

An ERCP was performed using an Olympus TJF 20 side viewing duodenoscope. At endoscopic examination she was found to have a stenotic Ampulla of Vater, which could not be cannulated with a ball tipped cannula. A pre-cut sphincterotomy was performed using a Wilson-Cook needle sphincterotome. The sphincterotomy was then enlarged using a 12 o'clock sphincterotome and a cholangiogram revealed no abnormality of the lower end of the bile duct and a bile duct of 6 mm diameter. Biopsies of the stenotic papilla were taken to exclude malignancy and this showed the presence of chronic inflammatory cells.

The patient complained of epigastric pain with commencement of oral fluids 4 h after the procedure. Physical examination revealed subcutaneous emphysema of the neck and mild systemic toxicity. Abdominal chest X-rays were performed and these showed the presence of extensive intraperitoneal and retroperitoneal gas (Fig. 2). The patient was fasted, and the nasogastric tube was inserted and a gastrograffin swallow was performed. This showed no evidence of leakage of contrast from the oesophagus or duodenum. The patient was commenced on intravenous Ampicillin, gentamycin and Metronidazole and closely monitored. A computed tomography (CT) scan

was performed to exclude a collection; this was reported as normal.

The serum amylase was initially 2365, but fell rapidly to normal range within 24 h. The liver function tests remained normal. Oral fluids were reintroduced after 96 h, and the patient was subsequently discharged well on the fifth postoperative day.

Case 2

A 59 year old woman was admitted with recurrent attacks of severe biliary pain following laparoscopic cholecystectomy 9 months earlier. The pain was associated with intermittent elevation of liver function tests: gamma-glutamyl transferase (GGT) ranged between 136 and 172 (range 11–60) prior to admission. A common bile duct calculus was suspected. The patient underwent ERCP using the Olympus TJF 20 duodenoscope using a ball tipped cannula; the cholangiogram showed a narrow common bile duct and intrahepatic ducts with no evidence of calculus. Following recurrent episodes of pain and multiple readmissions to hospital the patient was electively readmitted for endoscopic sphincterotomy.

A standard sphincterotome could not be introduced into the papilla of Vater. A pre-cut sphincterotomy was performed, using a Wilson-Cook needle sphincterotome. The patient was returned to the ward where she complained of severe epigastric pain in the immediate postoperative period. Abdominal X-ray showed pneumoperitoneum and retroperitoneal gas. There was a 50% right pneumothorax on chest X-ray. Serum amylase was 497 (10–220), gamma glutamyl transferase (GGT): 298 (11–60), aspartate amino transferase (AST): 82 (14–50) and analine amino transferase (ALT): 67 (11–60). The patient was fasted, a pleural drainage tube was inserted and intravenous Ampicillin, gentamycin and Metronidazole administered.

There was no evidence of continued duodenal leak on gastrograffin contrast examination. The liver function tests returned to a normal range over 48 h, apart from GGT which remained at three times the upper limit of normal.

The patient recovered rapidly and was discharged 5 days later. At her last review, 3 months following the procedure, she had occasional mild epigastric discomfort with considerable improvement on her pre-sphincterotomy symptoms.

DISCUSSION

The treatment of patients with suspected perforation of the duodenum following ERCP + ES presents a dilemma for the treating physician. It appears that the majority of ES-related perforations can be treated conservatively with intravenous fluids, parenteral nutrition and antibiotics[9,12,17] but the selection of patients for early surgery is not clear. There have been no deaths reported where patients have been treated conservatively, provided there has been no requirement for salvage surgery. If surgical treatment is ultimately required, the resultant mortality is high.[3]

It would appear, from the massed data, that the most important step is to identify those patients who require surgery early, in order to avoid inappropriate conservative therapy. The key to early identification of patients requiring surgery is suspicion, on the part of the treating physician, of the possibility of a perforation having occurred in any patient who complains of abdominal pain following ERCP + ES or in patients who have had a difficult ERCP + ES; particularly those who have required a pre-cut sphincterotomy. As shown by Sarr *et al.* the presence of pain following ERCP may be due to a number of possible causes including pancreatitis, cholangitis and perforation.[12] Patients who experience severe abdominal pain in the immediate post ES period accompanied by haemodynamic instability should be submitted for prompt investigation. All patients with suspected duodenal perforation should be fasted with nasogastric tube and intravenous fluids and close monitoring, while the investigations are performed.

The investigations should be carried out as quickly as possible once the suspicion of duodenal perforation has been raised. The investigations should include an erect and supine plain X-ray of the abdomen, a gastrograffin meal and a contrast-enhanced CT scan. In addition, the patient's full blood count, serum electrolytes, serum liver biochemistry and serum amylase should be performed. The free extravasation of contrast from the duodenum, on gastrograffin meal, indicates a persistent leak from an unsealed perforation and in the authors' opinion is an indication for surgical intervention. The site of perforation can sometimes be seen as a small dimple in the duodenal mucosa and in the absence of free extravasation this does not necessarily indicate the need for surgery. Lucas and Ledgerwood favoured gastrograffin swallow as the best means of demonstrating perforation in relation to blunt duodenal injury.[16] However, Sarr showed that there was free extravasation of the contrast in only one of five patients with post ERCP + ES perforation and concluded that the test was not reliable as a determinant of the presence of perforation, hence the need to perform a contrast CT scan.[12]

Kulhman *et al.* showed that CT scan is a very sensitive means of determining the presence of duodenal perforation.[1] CT signs such as pneumoperitoneum, retroperitoneal air bubbles in the fascial plane between the pancreas and the duodenum or a paraduodenal collection are indicators of duodenal perforation. Kulhman found that 31% of patients investigated for pain, fever or leukocytosis after ES had CT evidence of perforation. In the series by Sarr three patients were found to have paraduodenal collections on CT scan.[9] Sarr concluded that where there was not an objective indication of resolution of such a collection, surgical intervention was the safest course, with no ensuing mortality in his series.

From the experience of these two cases, the lack of extravasation of gastrograffin enabled conservative therapy. There was, undoubtedly, a small retroperitoneal perforation enough to allow large amounts of gas to extravasate under pressure, but not large enough for continued liquid contamination of the retroperitoneum. A CT scan may be more sensitive in detecting retroperitoneal emphysema and thus diagnosing perforation, but

contrast studies may better predict those patients with continued contamination and who are likely to benefit from surgery.

RECOMMENDATIONS

On the basis of the literature review conservative management would be recommended only in those patients with minimal clinical signs, normal white cell count and no pyrexia. All patients with clinical signs of sepsis, contrast leakage on imaging or paraduodenal collection should be considered for expeditious surgery. An experienced gastrointestinal surgeon should be involved in management from the time of suspicion of perforation.

REFERENCES

1. Kuhlman JE, Fishman EK, Milligan FD, Siegelman SS. Complications of endoscopic retrograde sphincterotomy: Computed tomographic evaluation. *Gastrointest. Radiol.* 1989; **14**: 127–32.
2. Safrany L, Cotton PB. Endoscopic management of choledocholithiasis. *Surg. Clin. N. Am.* 1982; **62**: 825–35.
3. Booth FV McL, Doerr RJ, Khalafir RS, Luchette FA, Flint LM. Surgical management of complications of endoscopic sphincterotomy with precut papillotomy. *Am. J. Surg.* 1990; **159**: 132–6.
4. Neuhaus B, Safrany L. Complications of endoscopic sphincterotomy and their treatment. *Endoscopy* 1981; **13**: 197–9.
5. Sherman S, Ruffolo TA, Hawes RH, Lehman GA. Complications of endoscopic sphincterotomy. *Gastroenterol.* 1991; **101**: 1068–73.
6. Hansell DT, Millar MA, Murray WR, Gray GR, Gillespie G. Endoscopic sphincterotomy for bile duct stones in patient with intact gallbladders. *Br. J. Surg.* 1989; **76**: 856–8.
7. Ghazia A, McSherry CK. Endoscopic retrograde cholangiopancreatography and sphincterotomy. *Ann. Surg.* 1984; **199**: 21–7.
8. Safrany L. Duodenoscopic sphincterotomy and gallstone removal. *Gastroenterology* 1977; **72**: 338–43.
9. Dunham F, Bourgeois N, Gelin M, Jeanmart J, Toussaint J, Cremer M. Retroperitoneal perforations following endoscopic sphinterotomy: Clinical course and management. *Endoscopy* 1982; **14**: 92–6.
10. Neoptolemos JP, Davidson BR, Shaw DE, Lloyd D, Carr-Locke DL, Fossard DP. Study of common bile duct exploration and endoscopic sphinterotomy in a consecutive series of 438 patients. *Br. J. Surg.* 1987; **74**: 916–21.
11. Koch H, Rosch W, Schaffner O, Demling L. Endoscopic papillotomy. *Gastroenterology* 1977; **73**: 1393–6.
12. Sarr MG, Fishman EK, Milligan FD, Siefelman SS, Cameron JL. Pancreatitis or duodenal perforation after perivaterian therapeutic endoscopic procedures: Diagnosis, differentiation and management. *Surgery* 1987; **100**: 461–6.
13. Ihre T, Hellers G. Complications and endoscopic retrograde cholangio-pancreatography. *Acta Chir. Scand.* 1977; **143**: 167–71.
14. Geenen JE, Vennes JA, Silvis SE. Resume of a seminar on endoscopic retrograde sphincterotomy (ERS). *Gastrointest. Endosc.* 1981; **27**: 31–8.
15. Byrnes DJ. Endoscopic sphincterotomy for bile duct gallstones. *Med. J. Aust.* 1983; 264–5.
16. Lucas CE, Ledgerwood AM. Factors influencing outcome after blunt duodenal injury. *J. Trauma* 1975; **15**: 846–9.
17. Leese T, Neoptolemos JP, Carr-Locke DL. Successes, failures, early complications and their management following endoscopic sphincterotomy: Results in 394 consecutive patients from a single centre. *Br. J. Surg.* 1985; **72**: 215–19.
18. Ponchon T, Valette PJ, Bory R, Bret PM, Bretagnolle M, Chavaillon A. Evaluation of a combined percutaneous-endoscopic procedure for the treatment of choledocholithiasis and benign papillary stenosis. *Endoscopy* 1987; **19**: 164–6.
19. Neoptolemos JP, Carr-Locke DL, London N, Bailey I, Fossard DP. ERCP findings and the role of endoscopic sphincterotomy in acute gallstone pancreatitis. *Br. J. Surg.* 1988; **75**: 954–60.
20. Shemesh E, Klein E, Czerniak A, Bat L. Endoscopic sphincterotomy in patients with gall bladder *in situ*: The influence of periampullary duodenal diverticula. *Surgery* 1990; **107**: 163–6.
21. Escourrou J, Cordova JA, Lazorthes F, Frexinos J, Ribet A. Early and late complications after endoscopic sphinterotomy for biliary lithiasis with and without the gall bladder 'in situ'. *Gut* 1984; **25**: 598–602.
22. Cotton PB, Vallon AG. British experience with duodenoscopic sphincterotomy for removal of bile duct stones. *Br. J. Surg.* 1981; **68**: 373–5.
23. Viceconte G, Viceconte GW, Pietropaolo V, Montori A. Endoscopic sphincterotomy: indications and results. *Br. J. Surg.* 1987; **68**: 376–80.
24. Cotton PB. Non-operative removal of bile duct stones by duodenoscopic sphincterotomy. *Br. J. Surg.* 1980; **67**: 1–5.
25. Vaira D, Ainley C, Williams S *et al.* Endoscopic sphincterotomy in 1000 consecutive patients. *Lancet* 1989; 431–3.
26. Safrany L. Endoscopic treatment of biliary diseases. *Lancet* 1978; 983–5.
27. Martin DF, Tweedle DEF. Retroperitoneal perforation during ERCP and endoscopic sphincterotomy: Causes, clinical features and management. *Endoscopy* 1990; **22**: 174–5.

Aust. N.Z. J. Surg. 1992, **62**, 969–972

LAPAROSCOPIC FUNDOPLICATION: A PRELIMINARY REPORT OF THE TECHNIQUE AND POSTOPERATIVE CARE

GREGORY L. FALK, ROY P. BRANCATISANO, JOHN HOLLINSHEAD AND JOHN MOULTON

Department of Upper Gastrointestinal Surgery, Concord Hospital, Sydney, New South Wales, Australia

The technique of laparoscopic fundoplication and its hospital management are described. Thirty day results in seven patients demonstrate the decreased insult to the patient, early discharge and early return to usual function, similar to that seen in laparoscopic cholecystectomy.

Key words: hospitalization, laparoscopic fundoplication.

Introduction

Laparoscopic surgery has evolved rapidly during the past 3 years. Numerous large series have demonstrated the safety, significantly reduced morbidity and duration of hospitalization resulting from this type of surgery. The laparoscopic technique now enables performance of laparoscopic cholecystectomy[1–3] large and small bowel resections, extraction of common bile duct (CBD) stones and the repair of inguinal hernias, in selected patients. A preliminary report of laparoscopic fundoplication for gastro-oesophageal reflux has been published by Dallemagne.[4]

Symptomatic gastro-oesophageal reflux (GER) is a common disorder. The indications for surgery in reflux are well established. A short, floppy total fundoplication has repeatedly shown superior results.[5,6]

We describe a laparoscopic technique for performing a floppy fundoplication similar to that achieved at open surgery.

Patients

Laparoscopic fundoplication was undertaken in eight patients. Medical management of symptomatic endoscopically proven reflux oesophagitis had failed in all the patients. All of the patients had at least grade 2 oesophagitis, but as initial endoscopy was not performed by the authors and all patients were on treatment, precise data are not available. Median age was 50 years with a range of 32–75 years. There were three females and five males. Six patients had continued symptoms on omeprazole and one had continued symptoms on H_2 antagonists. Five patients had unhealed oesophagitis after prolonged therapy and two patients had complications of pulmonary aspiration. All hernias were less than 4 cm in length.

The pre-operative, operative and postoperative data have been prospectively recorded in proforma.

Correspondence: Mr G. L. Falk, PO Box 1085, Strathfield, NSW 2135, Australia.

Accepted for publication 29 July 1992.

Technique

The operation is performed under general anaesthetic with the patient positioned in Lloyd-Davies stirrups. Intermittent compression stockings, subcutaneous heparin and anti-embolism stockings are used for deep venous thrombosis (DVT) prophylaxis. The operator stands between the legs of the patient with the camera operator on the left side of the table and the second assistant and nurse on the right side. The patient is positioned in steep reverse Trendelenberg.

After routine establishment of pneumoperitoneum, five 10 mm ports are inserted in the positions shown in Fig. 1.

The mid-line 10 mm port is used for access for the laparoscope while the superior laterally placed ports are the working ports. We principally use the wide angled forward viewing scope and the 30° scope when necessary. One can easily relocate the scope through another port for optimal visualization.

The surgical dissection of the hiatus is facilitated by lifting the left lobe of the liver away from the stomach. This is achieved by placing a retracting instrument through port #5 and retracting the left lobe of the liver upwards. The left triangular ligament is not divided as this provides a necessary anchor point for retraction.

The anatomy of the region as seen through the laparoscope is shown in Fig. 2. The left lobe of the liver is retracted upwards exposing the central tendon of the diaphragm, the phreno-oesophageal membrane, the lesser omentum and the stomach.

Fig. 1. Sites of port insertion.

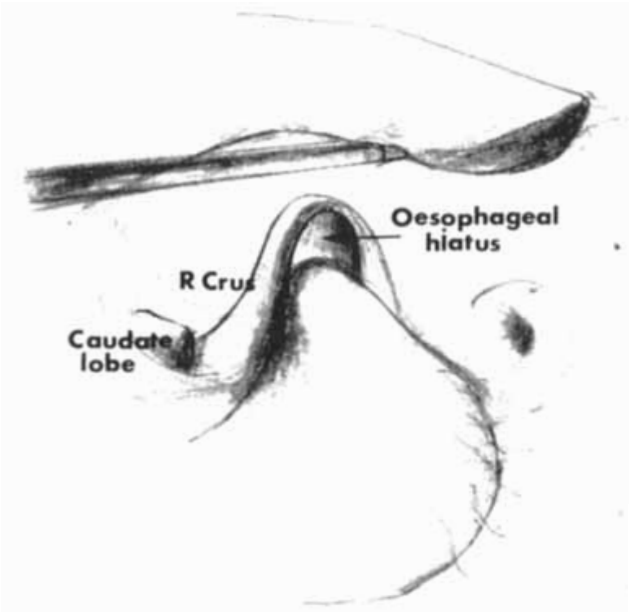


Fig. 3. Anatomy of the region. Incision of the phreno-oesophageal membrane.

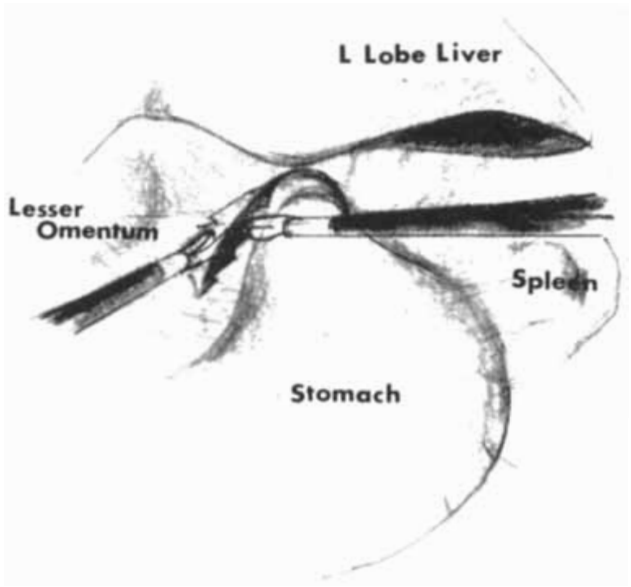


Fig. 2. Anatomy of the region. Incision of the lesser omentum.

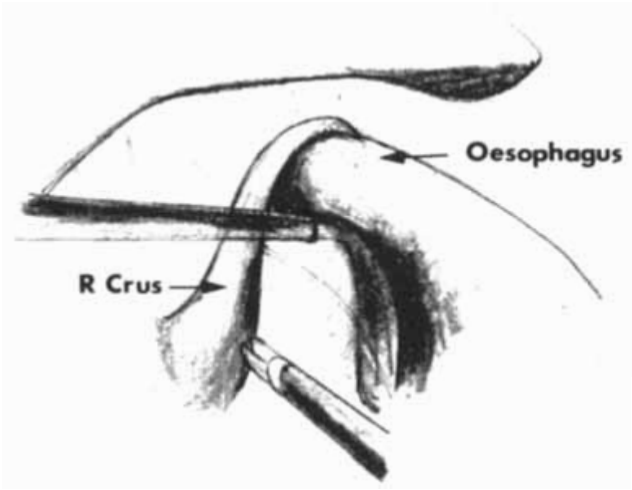


Fig. 4. Dissection of the right crus and mobilization of the posterior aspect of the oesophagus.

The dissection is commenced by incising the lesser omentum and dividing the phreno-oesophageal membrane over the anterior aspect of the crura, so exposing the apex of the hiatus. The hepatic vagal fibres are preserved (Figs 2, 3).

The right crus is cleared from the right lateral wall of the oesophagus (Fig. 4). The oesophagus is retracted upward with a grasping forcep placed in the left port while clearing the right crus with a forceps from the right working port.

This manoeuvre is reversed to mobilize behind the oesophagus using the left port forceps for dissection. The posterior trunk of the vagus nerve is displaced posteriorly. During this dissection care should be taken not to puncture the left pleura. Dissection is carried into the mediastinum to adequately mobilize the oesophagus into the abdomen. The crura are cleared to their origin posteriorly.

The dissection of the left crus and gastric cardia is performed next (Fig. 5). While performing this dissection, optimal visualization is occasionally achieved using the 30° side viewing scope. The gastric cardia is cleared and the short gastric vessels are clipped or suture ligated and divided as necessary to mobilize adequate fundus for a floppy wrap. This is performed using the left lateral and mid-line ports for instruments and the left subcostal port for the camera.

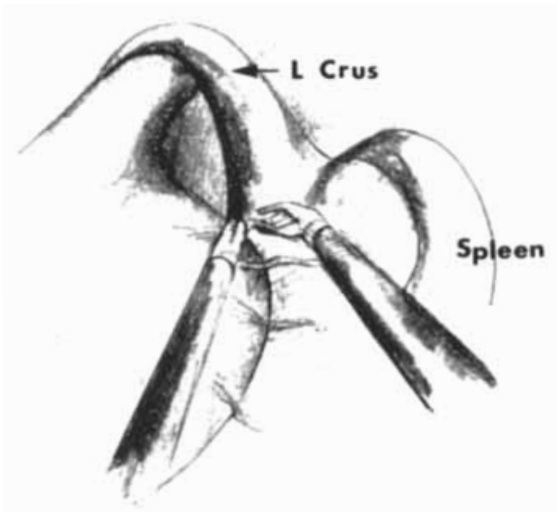


Fig. 5. Dissection of the left crus and gastric cardia. Division of the short gastric vessels.

Fig. 6. Suture of the hiatus.

Fig. 7. Positioning the fundic wrap.

Fig. 8. Suture of the fundoplication.

Once both crura and the oesophagus have been mobilized, one can assess whether the hiatus requires closure (Fig. 6). Hiatal repair is performed by approximating the crura with silk sutures while retracting the oesophagus anteriorly.

The right working forceps is guided behind the oesophagus and the mobilized fundus is grasped and drawn through behind the oesophagus (Fig. 7). With the posterior part of the wrap loosely lying in position, a complete 360° fundoplication is achieved by positioning the anterior fundus over the oesophagus (Fig. 8).

The fundoplication is sutured using two sutures of 2/0 black silk on a standard 26 mm curved needle incorporating the anterior wall of the oesophagus. Intracorporeal ties are performed. The fundoplication is calibrated with a 45–55 French bougie, and a 10 mm laparoscopic instrument is passed between wrap and oesophagus to ensure 'floppiness'.

Operative results

Seven of eight patients submitted to surgery were completed by laparoscopy. The first patient was quite obese and had an unsuspected para-oesophageal component. The dissection of the hiatus was difficult and vision was obscured by fat. Open completion was without problem.

The duration of the procedure has varied 1–7 h (median 3.5 h). The hiatus was repaired in two patients. Short gastric vessels were divided in three patients.

Postoperative course

A nasogastric tube was left overnight in the first two patients operated but as both had bowel sounds

the next morning, it was removed at the end of surgery in subsequent cases.

Bowel sounds were present at a mean of 12 h postoperatively (range: 8–20 h). Oral fluids were commenced the next morning (12 h) and soft diet at 24 h (16–28 h).

Mediastinal emphysema was present on postoperative chest X-ray in six patients. Cervical emphysema was identified intra-operatively in four cases, at which time insufflation pressures were reduced to 8–9 mmHg without exposure problems, to minimize the potential for pneumothorax.

Pneumothorax occurred intra-operatively in one patient and was identified immediately as the left pleura was perforated during dissection of the left crus. The patient's vital signs and monitoring did not change. This patient was a 33 year old fit male, the outcome may have been different in an older patient with respiratory disease. The pneumothorax was treated with a small intercostal catheter which was removed at 24 h without untoward sequelae. This is completely avoidable with experience.

Thirty day results

All seven patients achieved complete control of heartburn and regurgitation. Three patients suffered transient dysphagia (2–3 weeks) for solids and all completely resolved. All patients are able to belch from the abdomen.

Patients were discharged at a median of 48 h postoperatively and all had returned to normal activity by 2 weeks, which included golf but not heavy lifting.

Discussion

These data highlight the major advantages of laparoscopic surgery, namely early discharge, decreased patient discomfort and early return to normal activity.

The early results of laparoscopic floppy fundoplication in the present patients and those reported by Dallemagne are gratifying.

Long-term follow-up of symptom relief and objective review by endoscopy and 24 h pH study will be necessary to ensure full acceptance of this procedure, and is underway in a series to be presented in our next report.

The procedure described herein is based on the proven technique of the floppy 360° wrap which is established as the procedure of choice for the surgical management of severe gastro-oesophageal reflux disease.[5,6]

The operation within the abdomen is the same as 'open' surgery, but without the abdominal incision. There is no reason to believe that the medium or long-term symptomatic or objective results will be any different from those of 'open' floppy fundoplication.

References

1. Perissat J., Coller D. R. & Belliard R. (1989) Gallstones: Laparoscopic treatment, intra corporeal lithotripsy followed by cholecystostomy or cholecystectomy — a personal technique. *Endoscopy* **21**, 373–4.
2. Dubois F., Icard P., Berthelot G. & Levard H. (1990) Coelioscopic cholecystectomy. *Am. Surg.* **211**, 60–2.
3. Reddich E. J. & Olsen D. O. (1989) Laparascopic laser cholecystectomy: A comparison with mini-lap cholecystectomy. *Surg. Endosc.* **3**, 31–3.
4. Dallemagne B., Weerts J. M., Jehaes C. *et al.* (1991) Laparoscopic nissen fundoplication: Preliminary report. *Surg. Laparosc. Endosc.* **1**, 138–43.
5. DeMeester T. R., Johnson L. F. & Kent A. H. (1974) Evaluation of current operations for the prevention of gastro-oesophageal reflux. *Ann. Surg.* **180**, 511–25.
6. DeMeester T. R., Benavina L. & Albertucci M. (1986) Nissen fundoplication for gastroesophageal reflux disease. *Ann. Surg.* **204**, 9–20.

FUNDOPLICATURE PAR CŒLIOSCOPIE

G.L. Falk, R.I. Harrison, I. P. Adams, R.P. Brancatisano

Sydney

La fundoplicature laparoscopique fut réalisée pour la première fois en 1990 par Dallemagne. L'auteur, quant à lui, commença indépendamment la pratique de la fundoplicature laparoscopique la même année alors qu'il n'y avait qu'une petite expérience mondiale de cette technique, et depuis cette date il a réalisé 300 fundoplicatures laparoscopiques. Deux techniques opératoires différentes ont été utilisées durant deux périodes différentes. La première partie de la série comporte 50 patients (Groupe I); la deuxième partie de la série a été réalisée avec la technique décrite plus loin (Groupe II). Les résultats de la chirurgie se sont améliorés et le taux de complications a diminué en raison d'une expérience plus importante et de l'adoption de la technique du Groupe II.

MOTS CLÉS : **Fundoplicature, Laparoscopie.**

❒ MÉTHODE

Un dossier prospectif de tous les patients ayant subi une chirurgie antireflux a été constitué.

Le premier groupe de 50 patients a été opéré par laparoscopie avec une technique qualifiée de procédé Groupe I [2], la série suivante fut opérée selon une technique qualifiée de procédé Groupe II.

L'âge moyen des patients du Groupe I était de 49 ans (extrêmes 14-75) avec 64 % d'hommes. L'âge moyen du Groupe II était de 50 ans (extrêmes 14-82) avec 58 % d'hommes.

Un petit nombre sélectionné de patients a subi une chirurgie ouverte d'emblée lorsque la cœlioscopie était considérée comme vouée à l'échec et les observations de ces patients n'ont pas été incluses dans cette étude. Ces patients ont été exclus du traitement laparoscopique en raison d'antécédents de chirurgie gastrique ou pancréatique, d'obésité ou de brachy-œsophage associé à de grosses hernies.

Dans une étude séparée un observateur indépendant interrogea une cohorte consécutive de 100 patients du Groupe II pour apprécier le résultat symptomatique.

Une revue objective par endoscopie postopératoire et pHmétrie de 24 heures ne fut possible que chez respectivement 127 et 21 malades.

Une étude complémentaire de la symptomatologie clinique fut réalisée en 1996 chez 206 patients (cas 51 à 256) à titre d'évaluation des malades du Groupe II.

❒ TECHNIQUE

GROUPE I

Une manométrie préopératoire n'a été que rarement réalisée dans la première série. Tous les malades ont été opérés par cœlioscopie.

Les patients étaient installés en "French" position avec des étriers de lithotomie (Lloyd-Davis d'abord, et plus tard

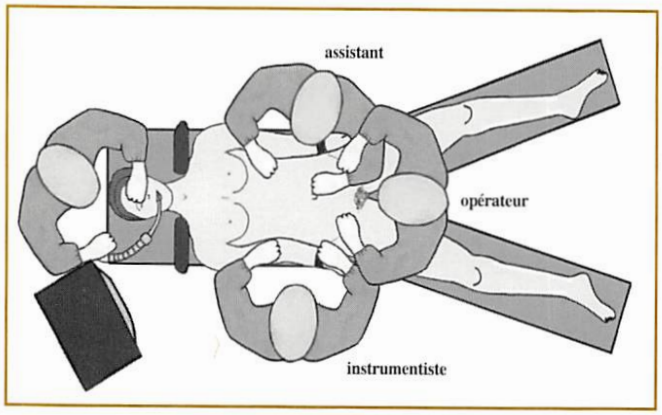


Fig. N° 1

étrier d'Allen). L'opérateur était entre les jambes du malade, l'instrumentiste à sa gauche et l'aide à sa droite (Fig. N° 1).

Cinq voies étaient installées de routine (Fig. N° 2), écarteur à foie (A), trocarts opérateurs (B, D), caméra (C), pince de l'assistant (E).

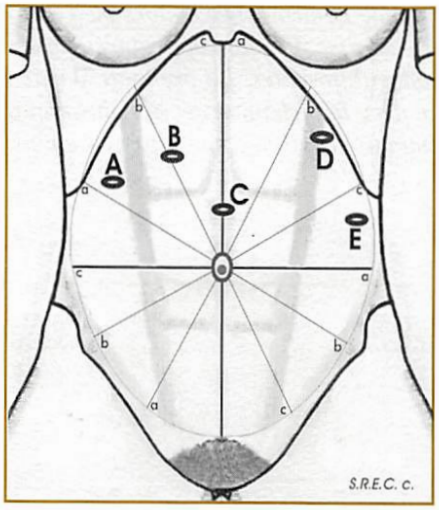


Fig. N° 2

La dissection commençait par l'hiatus. L'œsophage était disséqué sur toute sa circonférence et la hernie réduite dans l'abdomen. Les vaisseaux courts étaient sectionnés selon les besoins de l'intervention, l'hiatus suturé s'il était jugé large. Le fundus était passé autour de l'œsophage et fixé par des points de suture de soie, amenant le mur antérieur de l'estomac derrière l'œsophage.

Des nœuds intracorporels de soie 2/0 sertie d'une aiguille de 26 mm étaient noués pour donner une écharpe de 2 cm.

Une sonde naso-gastrique était mise en place et si nécessaire, un drain aspiratif.

Une alimentation liquide était reprise le matin suivant et le patient quittait l'hôpital 48 heures après.

GROUPE II

L'opération du Groupe II a différé de celle du Groupe I sur plusieurs points :

- Une manométrie préopératoire était demandée pour déterminer si l'on devait réaliser une fundoplicature totale ou partielle. En cas d'un défaut de 50% de la propagation d'une bouchée liquide ou si l'amplitude péristaltique était nettement inférieure à 20mmHg, une fundoplicature partielle postérieure était réalisée.
- Les critères de sélection pour une fundoplicature laparoscopique étaient l'absence de brachy-œsophage et d'antécédents de chirurgie gastrique ou pancréatique.
- Pour prévenir l'emphysème médiastinal la section des vaisseaux courts gastriques était entreprise d'emblée et a toujours été réalisée dans la technique Groupe II. La dissection et la libération du pourtour œsophagien en étaient ainsi facilitées.
- Les narcotiques per et postopératoires n'ont pas été employés en raison de leur action émétisante. Plus tard, l'*ondansetron* (Zophren) devint disponible et fut administré systématiquement en salle de réveil.

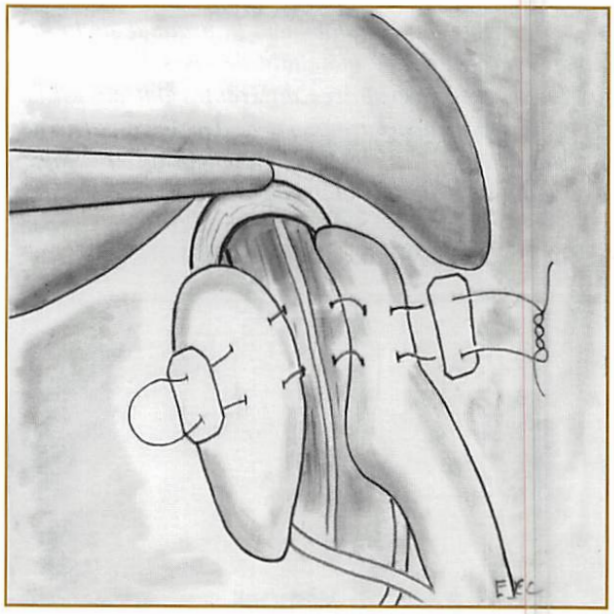
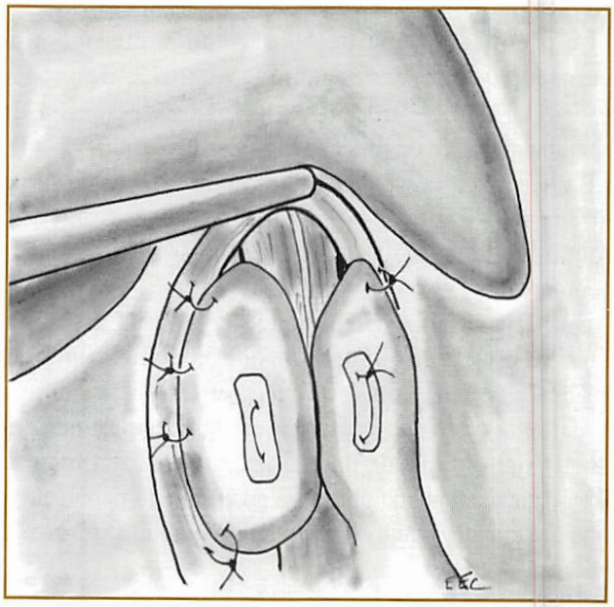


Fig. N° 3 *Fixation de la fundoplicature sur des patchs de teflon*



- La suture de l'hiatus était jugée obligatoire et une fermeture calibrée de l'orifice diaphragmatique était réalisée sur une bougie 50-60 French.

- La fundoplicature était, elle aussi, calibrée avec la bougie pour s'assurer qu'elle était suffisamment "lâche", puis fixée par une suture de Prolène 2/0 sur des patchs de teflon (Fig. N° 3) ainsi qu'au diaphragme et aux piliers en trois endroits (4, 7 et 11 heures).

- Un anti-inflammatoire non stéroïdien en suppositoire et un antalgique oral (*dextropropoxyphène*) était administrés au malade dès le réveil.

- En l'absence de nausées l'alimentation liquide était reprise 12 heures après l'opération. On ne laissait pas de sonde naso-gastrique, mais un drain sous - diaphragmatique était systématiquement mis en place et enlevé au bout de 24 heures.

❒ RÉSULTATS

Nous avons réalisé une fundoplicature laparoscopique chez 300 patients depuis la première tentative en 1990.

• ***Investigations***

Tous les patients ont eu une fibroscopie préopératoire. Sur les 206 cas consécutifs du Groupe II, entre juin 93 et décembre 95, une manométrie œsophagienne préopératoire a été réalisée chez 180 patients (91 %).

Cent-trente-cinq patients ont eu une pHmétrie de 24 heures (65 %).

Un transit baryté a été demandé en cas de suspicion de brachy-œsophage ou de hernie complexe.

INDICATIONS OPÉRATOIRES DES 206 FUNDOPLICATURES LAPAROSCOPIQUES (GROUPE II)		
Échec du traitement médical	132	64,1 %
Arrêt du traitement médical souhaité par le malade, malgré un bon contrôle	42	20,4 %
Hernie par roulement (mixte ou para-œsphagienne)	32	15,5 %

Tableau I

• ***Indications***

Chez les 206 patients du Groupe II, l'indication à la chirurgie a été l'échec du traitement médical 102 fois, le souhait du malade d'être débarrassé des médicaments malgré un bon contrôle 42 fois, l'existence d'une hernie complexe avec une composante de roulement 32 fois (Tableau I).

Dans ce group, 62 patients avaient une œsophagite en colonne prouvée par la biopsie.

PATHOLOGIE 206 FUNDOPLICATURES LAPAROSCOPIQUES (GROUPE II)		
Œsophagite "en colonne"	62	30,1 %
Manifestations pulmonaires	49	23,8 %
Hernie par roulement (mixte ou paraœsophagienne)	32	15,5 %
Sténose	18	8,7 %

Tableau II

Des manifestations pulmonaires représentaient un facteur aggravant chez 49 de ces patients. Il y avait une sténose peptique dans 18 cas (Tableau II).

• ***Complications***

Il y a eu une plaie viscérale chez deux patients parmi les 50 premiers cas, mais plus aucune par la suite.

Des complications postopératoires précoces sont survenues chez 13 patients (26 %) du Groupe I et chez 12 patients (6 %) du Groupe II ($P < à 0,01$)*. Le taux a été de 50 % chez les malades nécessitant une conversion en chirurgie ouverte.

Une insuffisance de l'hiatus est apparue chez 7 patients souffrant d'une récidive dans le Groupe I (14 %) et chez 2 patients dans le Groupe II (1 %) ($P < 0,01$)*. Deux des sept patients du Groupe I avec récidive présentaient un tableau de volvulus aigu. La récidive des 5 autres patients est survenue au bout de 30 jours.

• ***Conversions en chirurgie ouverte***

Parmi les 100 premières fundoplicatures laparoscopiques 11 conversions en chirurgie ouverte ont été nécessaires, la majorité (N = 8) dans les 50 premiers cas.

Les indications habituelles pour la conversion en chirurgie ouverte étaient les grosses hernies mixtes (N = 6), l'obésité (N = 2) et des antécédents de chirurgie gastrique (N = 3).

Ces conversions en chirurgie ouverte se sont accompagnées d'une importante morbidité avec des complications majeures chez 6 patients.

Après les 100 premiers opérés, nous n'avons plus le taux exact de conversion mais il est maintenant très bas.

Cette expérience a été utilisée pour sélectionner les patients du Groupe II pour une chirurgie ouverte directe : 8 patients ont été sélectionnés sur ces bases pour une chirurgie ouverte systématique en raison d'une hernie par roulement.

• ***Réinterventions***

Le taux de réinterventions chez les 50 premiers patients (Groupe I) a été de 20 %, 14 % pour récidive (aiguë ou secondaire) 4 % pour dysphagie et 2 % pour hernie sur orifice de trocart.

* *Chi-Square Test*

Le taux de réinterventions pour récidives a été réduit à 2 % chez les 100 patients suivants du fait de l'adoption de la technique Groupe II et à 0 % pour la troisième centaine, donnant un taux global de 0,8 % pour la technique Groupe II.

La hernie incisionnelle a nécessité une réparation chez 3 des 206 patients du Groupe II (1,5 %).

- ***Évaluation des symptômes (Groupe II)***

100 patients ont été interrogés avec un recul moyen de 18 mois. Une dysphagie transitoire postopératoire persistait au-delà de 6 semaines chez seulement 9 malades (9 %) et 2 patients présentaient une dysphagie permanente.

Un certain degré de distension gazeuse est apparu dans 7 % des cas.

La modification du grade Visick selon Goligher a servi de base pour évaluer les résultats : 76 patients étaient Visick I, 20 patients Visick II et 4 patients avaient un résultat non satisfaisant (2 Visick III et 2 Visick IV).

Le taux de succès est donc de 96 %.

- ***Évaluation objective postopératoire (Groupe II)***

Une fibroscopie postopératoire a été pratiquée chez 127 des 206 patients retenus dans le Groupe II : il n'y avait aucun cas d'œsophagite récurrente.

Seuls 21 patients ont accepté la pHmétrie post-opératoire. La pHmétrie ambulatoire de 24 heures a démontré une diminution du temps d'exposition acide qui était en préopératoire de 16 % ± 14,3 % (extrêmes 0,0 % - 73,6 %) chez 135 patients, à un taux postopératoire de 0,6 % ± 2,0 % chez 21 patients. Un malade présentait une élévation excessive asymptomatique de son exposition acide en position couchée (9,4 %). Le large éventail de l'exposition acide préopératoire reflète les scores très bas d'exposition acide préopératoire dans le groupe des malades ayant une hernie hiatale mixte ou para-œsophagienne. Le seul score très haut est secondaire à un épisode prolongé de reflux chronique gastro-œsophagien lorsque le patient restait couché.

DISCUSSION

La série décrite dans ce travail étudie le développement et l'évolution du procédé de fundoplicature laparoscopique réalisée par un seul opérateur (et représente la compilation de plusieurs analyses réalisées en 1993, 1994 et 1995).

Les difficultés d'introduction de la technique de la fundoplicature laparoscopique apparaissent à l'évidence ; en effet on constate la diminution du taux de complications et du taux de réinterventions à mesure que la série a progressé.

La technique Groupe I incorpore les éléments de deux techniques différentes, l'opération de Nissen standard [5] et la fundoplicature lâche "floppy" [6, 7].

En réalisant chez les 50 premiers patients une écharpe lâche, la partie haute de l'estomac était bien mobilisée.

Le défaut de suture de l'hiatus, du fait d'une mauvaise estimation de la taille de l'hiatus en cœlioscopie, a favorisé le taux élevé de récidives herniaires. Ce phénomène a été décrit par d'autres auteurs [8].

La technique Groupe II, avec mesure obligatoire et fermeture de l'hiatus, a quasiment éliminé la récidive herniaire. L'utilisation de l'*ondensetron* comme anti-émétique a supprimé les vomissements postopératoires et a contribué, nous le pensons, à la réduction du taux de récidives précoces.

Nous avons choisi de réaliser une écharpe "lâche" dans le but d'éliminer la dysphagie postopératoire, plutôt que le Nissen traditionnel avec son taux élevé d'effets secondaires [6].

Il est évident qu'en réalisant une technique "lâche" la suture de l'hiatus est obligatoire. La raison initiale pour nous de ne pas suturer l'hiatus était que, sous insufflation, le diaphragme est mis sous tension et que l'hiatus apparaît petit. Notre souci initial, en observant l'ouverture apparemment petite de l'hiatus, était de ne pas le fermer de peur de trop le rétrécir. Le fait que cela ait été une illusion a bien été démontré par les résultats de la fermeture calibrée de l'hiatus en utilisant une bougie œsophagienne.

Les résultats de l'évaluation symptomatique endoscopique, et la pHmètrie de 24 heures démontrent la capacité de cette procédure à contrôler correctement le reflux chez les patients du Groupe II sans incidence élevée de troubles secondaires gênants.

Les résultats de l'expérience de cette série sont analogues à ceux des autres grandes séries rapportées [9, 11, 12] montrant que la chirurgie laparoscopique du reflux donne d'excellents résultats précoces entre les mains de chirurgiens experts.

Bien qu'une étude des résultats à long terme soit nécessaire, nous pouvons prédire qu'il ne seront pas notablement différents de ceux de la chirurgie ouverte équivalente [6, 7], en considérant les résultats à court et moyen termes rapportés ici et ailleurs [9, 10 11, 12].

La morbidité de 6 % dans l'opération Groupe II est nettement plus basse que les 13 % du rapport de DeMeester dans une série de chirurgie ouverte [7]. A condition que le taux de récidive tardive reste bas, la fundoplicature laparoscopique devrait devenir la procédure de choix pour la chirurgie antireflux.

La courbe d'apprentissage est longue et l'opération requiert une maîtrise laparoscopique "avancée" [12]. C'est pourquoi il semblerait que les meilleurs résultats soient le fait d'une grande expérience.

La contribution aux bons résultats du Groupe II de l'évaluation en laboratoire n'a pas été quantifiée ; mais notre impression est qu'elle est importante et représente une caractéristique commune à beaucoup de grandes séries d'opérations antireflux [7, 9, 10, 11, 12].

CONCLUSION

La fundoplicature laparoscopique selon notre procédure Groupe II contrôle la maladie du reflux sévère avec une morbidité, une mortalité, et des effets secondaires acceptables dans le court terme. Une fermeture calibrée de l'hiatus diaphragmatique est nécessaire et vigoureusement recommandée, comme l'usage d'anti-émétiques dans la période périopératoire.

L'étude des résultats à long terme est cependant nécessaire pour l'évaluation de cette procédure.

Concord Hospital
A teaching Hospital of University of Sidney
Sidney NSW 2006 - Australie

Correspondance :
G.L. Falk, Director
Sydney Œsophageal Services
PO Box 1085
Strathfield NSW 2135 - Australie

RÉSUMÉ

La technique de fundoplicature par voie ouverte ou par laparoscopie n'a pas été standardisée, en particulier en ce qui concerne la fermeture de l'hiatus diaphragmatique et la section des vaisseaux courts gastriques. La difficulté rencontrée dans l'abord laparoscopique a conduit certains chirurgiens à modifier la technique qu'ils utilisaient en laparotomie pour réaliser la fundoplicature laparoscopique (F.L.). Une étude prospective de tous les patients ayant eu un F.L. a été réalisée. Le résultat fonctionnel d'une série consécutive de 100 patients a été étudié. Une analyse objective, concernant l'endoscopie et la pHmétrie ambulatoire, ne concerne qu'une partie des patients. L'indication principale de la chirurgie est l'échec du traitement médical. Le taux de complications de la chirurgie passe de 26 % (Groupe I) à 6 % (Groupe II) où la technique a été modifiée. Une insuffisance de l'hiatus est survenue chez 14 % des patients du Groupe I et chez seulement 1 % de ceux du Groupe II. Le taux de réintervention est passé de 20 % (Groupe I) à 0,8 % (Groupe II). Un excellent contrôle symptomatique du reflux a été obtenu dans le Groupe II. Les modifications de technique entre l'opération Groupe I et l'opération Groupe II, c'est à dire fermeture de l'hiatus et section généreuse des vaisseaux courts gastriques, ont amélioré les résultats. Les résultats de la F.L. à moyen terme sont excellents et peuvent être comparés à ceux de la chirurgie ouverte.

SUMMARY

The technique of open laparoscopic fundoplication has not been standardised, especially regarding the closure of the diaphragmatic hiatus and division of the short gastric vessels. The difficulty of the laparoscopic technique has led somme to modify their preferred "open" technique when performing laparoscopic fundoplication. A prospective record of all patients having laparoscopic fundoplication was kept. Symptomatic outcome of a consecutive series of 100 patients was reviewed. Limited objective review is reported, of endoscopy and ambulatory pH analysis. The predominant indication for surgery remained failure of medical therapy. Complication rates of surgery fell from 26 % (Group I) to 6% (Group II). Hiatal failure occured in 14 % of Group I patients and in the later group, 1 %. Re-operation rates fell from 20 % in the Group I operation to 0.8 % in the Group II operation. Excellent symptomatic control of reflux was obtained (Group II). Changes in techniques between the GroupI operation and Group II operation, namely hiatal repair and generous short gastric division were associated with much improved results. The medium term results of laparoscopic fundoplication are excellent and compare favourably with open series.

KEY WORDS : Fundoplication, Laparoscopy.

BIBLIOGRAPHIE

1 - DALLEMAGNE B., WEERTS J.M., JEHAES C., GROUPIEWICZ S., LOMBARD R. : Laparoscopic Nissen fundoplication : Preliminary report : *Surg. Endosc., 1991, 1, 138-143.*

2 - FALK G.L., BRANCATISANO R.P., HOLLINSHEAD J.W., MOULTON J. : Laparoscopic fundoplication : A preliminary report of the technique and postoperative care : *Anzj. Surg., 1992, 62, 969-972.*

3 - MUNRO W., BRANCATISANO R., ADAMS I.P., FALK G.L. : Complications of laparoscopic fundoplication : The first 100 patients : *Surg. Laparosc. and Endosc., 1996, 6, 421-423.*

4 - GOLIGHER J.C., PULNERTAFT C.N., DEDOMBAL F.T. et al. : Five to eight year results of Leeds/York controlled trial of elective surgery for duodenal ulcer : *Brit. Med. J., 1968, 2, 781-787.*

5 - NISSEN R. : Gastropexy and fundoplication in surgical treatment of hiatal hernia : *Am. J. Dig. Dis., 1961, 6, 954-961.*

6 - DONAHUE P.E., SAMELSON S., NYHUS L.M., BOMBECK C.T. : The floppy Nissen fundoplication. Effective long term control of pathologic reflux : *Arch. Surg., 1985, 120, 663-668.*

7 - DEMEESTER T.R., BONAVINA L., ALBERTUCCI M., NISSEN R. : Fundoplication for gastrœsophageal reflux disease. Evaluation of primary repair in 100 consecutive patients : *Ann. Surg., 1986, 204, 9-20.*

8 - WATSON D.I., JAMIESON G.G., DEVITT P.G., MITCHELL P.C., GAME P.H. : Para œsophageal hiatus hernia : an important complication of laparoscopic Nissen fundoplication : *B.J.S., 1995, 82,521-523.*

9 - WEERTS J.M., DALLEMAGNE B., HAMOIR et al : Laparoscopic Nissen fundoplication : detailed analysis of 132 patients : *Surg. Laparosc. Endosc., 1993, 3, 359-364.*

10 - JAMIESON G.G., WATSON D.I., BRITTEN-JONES R., MITCHELL P.C., ANVARI N. : Laparoscopic Nissen fundoplication : *Am. J. Surg., 1994, 220, 137-145.*

11 - HINDER R.A., CHARLES J. et al : Laparoscopic Nissen fundoplication is an effective treatment for gastroesophageal reflux disease : *Ann. Surg., 1994, 220, 4, 472-483.*

12 - GOTLEY D.C., SMITHERS B.M., RHODES M. et al : Laparoscopic Nissen fundoplication : 200 consecutive cases : *Gut, 1996, 38, 487-491.*

Les auteurs tiennent à adresser toute leur gratitude au Professeur David Gillett pour ses conseils pendant dix-sept ans de chirurgie, et leurs remerciements à Madame Alison Nunn pour l'aide apportée dans la réalisation de ce manuscrit.

EXTRA-OESOPHAGEAL REFLUX DISEASE: physiology, investigation and treatment

Reflux disease may present typically with heartburn regurgitation and dysphagia, or atypically with symptoms arising in the head and neck, throat and lungs. Diagnosis of typical disease has largely been facilitated by physiological study using pH catheters in the oesophagus. Outside the oesophagus technology has been poor to identify the patients with atypical symptoms which can be caused by multiple different alternative disease processes.

Attempts to quantify and qualify reflux disease by scintigraphy have been undertaken for the last 50 years. These studies were largely superseded by endoscopy and tube-based reflux studies such as 24 hour pH, and these became the diagnostic criteria for standard disease. Such diagnostic criteria were predicated upon patients who suffered heartburn and abnormal values were established in this patient group. By nature of this, such criteria were not appropriate to patients with atypical symptomatology. The tests suffered other inaccuracies, endoscopy being sensitive to reflux disease in only 30%, and tube-based testing largely dependent on being able to identify acid as the marker of the reflux event until recently. No techniques adequately tested for reflux fluid outside the oesophagus and normal values for patients with atypical reflux symptoms were not adequately established. Nonetheless patients without heartburn suffered inconspicuous clinically regurgitation events which caused considerable extra oesophageal symptomatology and morbidity. Patients may develop chronic chest infections, pulmonary damage such as bronchiectasis, late onset asthma, cough hypersensitivity syndrome and possibly a proportion suffered crippling pulmonary fibrosis. Additionally pulmonary reflux contamination in lung transplantation was thought to contribute to graft loss and death.

Patients with extra oesophageal symptomatology were referred to my diagnostic and therapeutic

service and found not to have “real” reflux disease by then current technology. A real need to accurately diagnose such disease required an adequate diagnostic testing schedule, as the current algorithm was inaccurate, time consuming, and expensive and frequently did not aid the patient. Diagnosis and management of this patient group required multiple attendances to different specialist groups, ENT respiratory medicine and gastroenterology to follow a process of exclusion. No individual specialist group was able to positively diagnose extra oesophageal reflux and the testing regimens were intrinsically unsound as there was no way to interrogate the extra oesophageal organs directly. Diagnosis remained either indicative only, or highly insensitive. Ad hoc bronchial lavage and pulmonary pepsin raised the suspicion that gastro- oesophageal reflux contamination of the lung and ear nose and throat area did exist in some patients, severe regurgitation could be identified by history, but the vast majority of patients did not have typical reflux symptoms.

It was apparent that the extra-oesophageal symptomatic patient group required a diagnostic test to enable adequate therapy, to identify the physiological characteristics which made the presenting symptomatology so different from simple heartburn. The use of the 24-hour pH probe device was largely applicable only to those patients with heartburn as this was its design and for which normal values obtained. A technique was required which interrogated extra oesophageal sites directly for the presence of gastric content. Previous techniques of gastric pepsin had suggested the presence of gastric regurgitation in the lung, head and neck, but sensitivity and specificity seemed poor. Invasive sampling was required to improve accuracy.

Scintigraphy had the potential to demonstrate gastrointestinal content in the oesophagus, pharynx, larynx, nasal cavity, eustachian tubes and lungs independent of pH values. This was only possible with the advent of new nuclear medicine technology (SPECT/ CT scanning and computerised reporting) and precise management of isotope kinetics. With the extended collaboration of my colleague Hans Van Der Wall we initially conceived the test. Serial

improvement in technique proceeded over half a decade, and to date is now able to identify patients with this different form of reflux disease.

Patients with heartburn related reflux events suffer multiple frequent episodes of acid reflux into the lower third of the oesophagus and very infrequently proximately. Patients with extra oesophageal proximal symptoms in the pharynx and larynx sinuses and lung suffered less frequent regurgitation events, no heartburn, and the events much more frequently entered the upper oesophagus and pharynx or lung. The availability of such a diagnostic test allowed tailored management of the patient and facilitated investigation of the abnormal physiology which brought about the symptoms. The application of this testing will be likely to enable further investigation , in an accurately diagnosed patient cohort, establishing the physiological abnormalities of this disease and the extent of disease.

This is the first such time that an adequate sensitive accurate test has been able to identify the presence of gastric fluid outside of the oesophagus. Symptom diagnosis is quite inaccurate and there are no other gold standard tests for extra-oesophageal reflux or laryngopharyngeal reflux disease (LPR) as this situation is frequently known. While scintigraphy appears essential for diagnosis it will also be an aid for patient selection for trials of management and therapy in the longer term. Previously patient selection had to rely upon symptomatology which was quite inaccurate.

Currently patients often see multiple specialists and it takes many years for a final diagnosis of LPR and then management. This diagnostic testing is likely to reduce needless repeated consultations in various specialist areas of medicine and repeated non-contributory testing. This symptomatology affects between 5 and 8% of the western adult population and so constitutes a very major health problem. A simplified technique for diagnosis and then management would be highly advantageous to the patient and to the costs of healthcare. It currently has and is likely to continue to improve the outcome of individual patient's and simplify management on an

increasingly frequent basis.

The studies have been verified against conventional oesophageal physiology of 24 hour pH and impedance reflux studies, oesophageal manometry, and endoscopy, in my laboratory. The validity of the diagnosis has been tested against surgical therapy and reported in the body of work. Normal values have been established.

Utilising the later understanding of the physiology of the reflux episode based on impedance reflux monitoring it became evident that multiple reflux episodes were non-acidic and that the reflux episode became less acidic as it travelled proximately in the oesophagus by neutralisation with saliva. The current standard of 24 hour pH study was thereby shown not to be of value in assessment of proximal reflux disease due to the lack of proximal acid events to measure. Impedance studies were repeatedly described inaccurately in the pharynx, leaving only scintigraphy as a positive diagnostic facility. It would appear that the digestive enzymes and acid component was substantially integral to the development of atypical symptoms.

The establishment of a diagnostic test which shows pulmonary contamination will allow developmental understanding and therapy of chronic cough, lung fibrosis, bronchiectasis, recurrent chest infections and possibly improved outcome of lung transplantation. This area has hitherto been outside any possibility of accurate diagnosis until now. Application of this developmental technology could have great significance in the improvement of pulmonary medical outcome in multiple fields of pulmonary disease.

The multiple publications developing the validity of this testing regimen and the physiology of atypical reflux disease, have been part of the PhD endeavours of Leticia Burton, Dr Oleksander Khoma, Dr Scott Simpson, and Dr Jin Soo Park through the University of Notre Dame

Oesophageal manometry and multichannel pH and impedance reflux studies have been undertaken identifying the physiological causes of extra-oesophageal reflux disease, Multiple metrics have

been assessed for value in the diagnosis of extra-oesophageal disease including in the pharynx. We have introduced the very newest technology as it has become available in the study of physiology and evaluated the metrics against scintigraphy, which has allowed description of the disease process of extra-oesophageal reflux/LPR. The association of abnormal peristaltic function in the oesophagus and the presence of extra-oesophageal disease has been identified. The association of gastric dysmotility with regurgitation events has become apparent. This work constitutes part of the PhD program at Notre Dame University of Dr Jin-soo Park. The new metrics have been evaluated in atypical reflux patients to establish usual criteria of abnormality in this patient group. It has strongly indicated that a series of previously nebulous respiratory and ear nose and throat diagnoses such as cough variant asthma and hypersensitivity cough are all strongly linked to the silent, but now physiologically recognised, extra- oesophageal regurgitation episode.

The practice of diagnosis in this area nationally and internationally has been influenced by this work being mentioned in editorial in Lung, correspondence with many world experts, an invitation to present this work in the UK in 2016 as visiting Professor. There has been uptake of this technology in several major centres around Australia and considering the early phase development of this technology further expansion is more than likely.

References:

1. Park J-s, Van der Wall H, Falk GL. Conventional and simple methods of measuring esophageal nocturnal baseline impedance show excellent agreement. Journal of Digestive Diseases. 2021;22(7):419- 24.

2. Park JS, Khoma O, Burton L, Van der Wall H, Falk GL. A new diagnostic paradigm for laryngopharyngeal reflux disease: correlation of impedance-pH monitoring and digital reflux scintigraphyresults. Eur Arch Otorhinolaryngol. 2021.

3. Park J-s, Burton L, Wall H, Falk G. Modified Reflux Scintigraphy Detects Pulmonary

Microaspiration in Severe Gastro-Esophageal and Laryngopharyngeal Reflux Disease. Lung. 2021;199.

4. Khoma O, Burton L, Falk MG, Van der Wall H, Falk GL. Predictors of reflux aspiration and laryngo-pharyngeal reflux. Esophagus. 2020;17(3):355-62.

5. Falk GL, Gooley SC, Church NG, Rangiah DS. How effective is the control of laryngopharyngeal refluxsymptoms by fundoplication? Symptom score analysis. European Surgery. 2020;52(3):123-6.

6. Burton L, Beattie J, Falk GL, Van der Wall H, Coman W. The burden of gastroesophageal reflux disease on the cost of managing chronic diseases in Australia. The need for a new diagnostic and management paradigm. Chronic Illness. 2020:1742395320966373.

7. Khoma O, Mendu MJ, Sen AN, Van der Wall H, Falk GL. Reflux Aspiration Associated withOesophageal Dysmotility but Not Delayed Liquid Gastric Emptying. Digestive Diseases. 2020.

8. Burton L, Joffe D, Mackey DW, Van der Wall H, Falk GL. A transformational change in scintigraphic gastroesophageal reflux studies: A comparison with historic techniques. Clin Physiol Funct Imaging. 2021;41(2):136-45.

9. Burton L, Falk GL, Beattie J, Novakovic D, Simpson S, Van der Wall H. Findings from a novel scintigraphic gastroesophageal reflux study in asymptomatic volunteers. Am J Nucl Med Mol Imaging.2020;10(6):342-8.

10. Burton L, Baumgart K, Novakovic D, Beattie J, Joffe D, Falk G, et al. Fungal Pneumonia in TheImmunocompetent Host: A Possible Statistical Connection Between Allergic Fungal Sinusitis with Polyposis and Recurrent Pulmonary Infection Detected by Gastroesophageal Reflux Disease Scintigraphy. Molecular imaging and radionuclide therapy. 2020;29(2):72-8.

11. Burton L, Falk GL, Baumgart K, Beattie J, Simpson S, Van der Wall H. Esophageal Clearance in Laryngopharyngeal Reflux Disease: Correlation of Reflux Scintigraphy and 24-hour Impedance/pH in aCohort of Refractory Symptomatic Patients. Mol Imaging Radionucl Ther.

2020;29(1):7-16.

12. Burton L, Falk GL, Parsons S, Cusi M, Van Der Wall H. Benchmarking of a Simple ScintigraphicTest for Gastro-oesophageal Reflux Disease That Assesses Oesophageal Disease and Its Pulmonary Complications. Molecular imaging and radionuclide therapy. 2018;27(3):113-20.

13. Khoma O, Falk SE, Burton L, Van der Wall H, Falk GL. Gastro-Oesophageal Reflux and Aspiration: Does Laparoscopic Fundoplication Significantly Decrease Pulmonary Aspiration? Lung. 2018;196(4):491-6

14. Falk GL, Vivian SJ. Laryngopharyngeal reflux: diagnosis, treatment and latest research. EuropeanSurgery. 2016;48(2):74-91.

15. Falk M, Van der Wall H, Falk GL. Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms.Nucl Med Commun. 2015;36(6):625-30.

16. Falk GL, Beattie J, Ing A, Falk SE, Magee M, Burton L, et al. Scintigraphy in laryngopharyngeal andgastroesophageal reflux disease: a definitive diagnostic test? World J Gastroenterol. 2015;21(12):3619- 27.

Received: 11 February 2021 | Revised: 18 May 2021 | Accepted: 24 May 2021

DOI: 10.1111/1751-2980.13024

ORIGINAL ARTICLE

Journal of Digestive Diseases WILEY

Conventional and simple methods of measuring esophageal nocturnal baseline impedance show excellent agreement

Jin-soo Park[1,2] | Hans Van der Wall[2,3] | Gregory Leighton Falk[1,4]

[1]Department of Surgery, Concord Repatriation General Hospital, Sydney, New South Wales, Australia

[2]University of Notre Dame, Sydney, New South Wales, Australia

[3]CNI Molecular Imaging, Meadowbank, Sydney, New South Wales, Australia

[4]University of Sydney, Sydney, New South Wales, Australia

Correspondence
Jin-soo Park, Suite 29, 12-18 Tryon Road, Lindfield Sydney, NSW 2070, Australia.
Email: jinsoo.park@health.nsw.gov.au

Objectives: Mean nocturnal baseline impedance (MNBI) shows promise in investigating reflux disease by reflecting esophageal mucosal integrity. This study aimed to measure MNBI by both conventional and simple methods in patients with laryngopharyngeal reflux (LPR) and gastroesophageal reflux disease (GERD) in order to evaluate the efficacy of the simple measurement method.

Methods: Altogether 187 patients were divided into LPR (n = 105) or GERD (n = 82) groups according to their predominant symptom profile, and underwent off-therapy impedance-pH monitoring. MNBI was measured by both the conventional and simple methods. The Bland-Altman plots were constructed to assess mean differences and to identify bias in the two measurement methods.

Results: For the two measurement methods, mean difference was (−89 ± 328) Ω in the distal esophagus, (−6 ± 653) Ω in the proximal esophagus, and (128 ± 577) Ω in the pharynx, respectively. There was a strong correlation between conventional and simple MNBI values, with the coefficient of 0.940 in the distal esophagus, 0.463 in the proximal esophagus, and 0.712 in the pharynx (all $P < 0.001$).

Conclusions: There was an excellent agreement between the conventional and simple methods of MNBI measurement, with no evidence of proportional bias. Conventional and simple MNBI values correlated excellently in the distal esophagus and moderately well in the proximal esophagus and pharynx. This study supports the use of the simple method of measuring MNBI to enhance diagnoses of reflux disease.

KEYWORDS
electrical impedance, esophageal mucosa, gastroesophageal reflux, heartburn, laryngopharyngeal reflux

1 | INTRODUCTION

Esophageal multichannel intraluminal impedance (MII)–pH monitoring has been used for the assessment of gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux (LPR) in clinical practice. Esophageal MII-pH detects changes in electrical impedance caused by reflux and swallows at multiple points along a catheter in the esophagus and can distinguish all reflux events as being gas or liquid, and as acidic or non-acidic. Between reflux events and swallows, the esophageal lumen is collapsed, and the baseline impedance is determined from the collapsed esophageal mucosa in contact with the electrodes. Increased acid exposure has been shown to reduce baseline impedance.[1,2]

Mean nocturnal baseline impedance (MNBI) is a novel measurement of baseline impedance during nocturnal recumbence, when tracings are less affected by swallows and reflux events.[2] MNBI has been shown to increase diagnostic yield in patients with GERD,[3] distinguish GERD patients who respond to proton pump inhibitors from those with functional heartburn[2] and predict improvements in symptomatic severity.[4]

Most recent studies have measured MNBI using the conventional method, which manually measures MNBI values at three stable 10-minute periods during the nocturnal recumbence that are free of reflux and swallow events.[2] This conventional MNBI measurement is time-consuming. Furthermore, the three 10-minute sampling periods do not completely represent the whole recumbent baseline period. Recently, a simple method of MNBI measurement has been described, where the average impedance of the whole nocturnal recumbence period was calculated. This method has been introduced as a faster and less selective way of obtaining MNBI, and is representative of the whole nocturnal recumbent period. In this study, MNBI values obtained by conventional and simple methods strongly correlated.[5] To our knowledge, no other studies have yet validated the simple MNBI measurement method. Therefore, the aim of the present study was to correlate MNBI values obtained by the conventional and the simple methods in patients with either GERD or LPR.

2 | PATIENTS AND METHODS

2.1 | Patient selection and study design

Consecutive patients with severe LPR and GERD were referred to a tertiary reflux treatment unit. The patients had failed medications and had undergone multidisciplinary investigation of differential diagnoses prior to their referral. The patients were divided by their predominant symptoms into either the GERD or the LPR group. Patients with LPR had a high pre-test probability of disease in the context of previous extensive investigation.

Data were extracted from a research database with current approval by the Sydney Local Health District Human Research Ethics Committee (reference number: LNR/12CRGH/248). The patients had given their written informed consent before their enrollment for the study of data under the Institutional Ethics Committee guidelines.

2.2 | MII-pH measurement

All patients underwent dual 24-hour MII-pH monitoring. Proton pump inhibitors were ceased for 5 days prior to the measurement. The anatomical locations of the upper esophageal sphincter (UES) and lower esophageal sphincters (LES) were manometrically defined. Following the topical application of nasal local anesthetic, a 2.3-mm naso-esophageal catheter (Zephyr; Sandhill Scientific Inc., Highlands Ranch, CO) was inserted. Six electrodes, which were 5, 7, 12, 14, 26 and 27 cm above the LES (z6, z5, z4, z3, z2 and z1, respectively), were used to measure the impedance, with the two uppermost electrodes measuring hypo-pharyngeal impedance. Two electrodes measured the pH value at the proximal and distal esophagus. No dietary or activity restrictions were required other than the ingestion of acidic beverages. The probe was connected to an external monitoring Zephyr device which collected data over the 24-hour period.

A decrease in impedance of 50% relative to the baseline, followed by an increase back to at least 50% of the baseline, traveling in a retrograde fashion, defined a reflux event. The most proximal channel that detected the drop in impedance defined whether the reflux event was distal, proximal or pharyngeal. Each reflux episode was classified as either acidic (pH <4) or non-acidic (pH ≥4). The acid exposure time (AET) was the total time that the pH value was <4, divided by the total measurement time, expressed as a percentage.

2.3 | MNBI measurement

The nocturnal recumbent period was identified in a 24-hour MII-pH reflux trace. Using Martinucci's conventional method, MNBI was measured by identifying three 10-minute intervals during the nocturnal recumbent period that were free of refluxes, swallows, or other signals were selected, typically at 01:00 AM, 02:00 AM and 03:00 AM. The baseline impedance for these three periods were obtained, the mean value of which was calculated as the conventional MNBI value. Using the Hoshikawa's simple method,[5] MNBI was measured by selecting the entire nocturnal recumbent period and obtaining the mean baseline impedance for the whole period (Figure 1). For both conventional and simple methods, MNBI was measured in the distal esophagus close to 5 cm above the LES (z6), in the proximal esophagus (14 cm above the LES) (z3) and in the pharynx (27 cm above the LES) which was 2 cm above the upper border of the UES (z1). Measurements by the conventional and simple methods were performed by one single author (J.S.P.) who was blinded to the symptoms and impedance-pH summaries of the patients.

2.4 | Statistical analysis

All the statistical analyses were performed by using the SPSS Statistics version 24.0 (IBM, Armonk, NY). The normal distribution of data was determined by using the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation and were analyzed by using the independent *t*-test, whereas categorical variables were expressed as numbers and percentages or frequencies and were analyzed with the χ^2 test. Correlations between continuous variables was tested using the Pearson's product-moment correlation coefficient (*r*).

The difference between each pair of the conventional and simple MNBI values was calculated. A difference close to zero denoted strong agreement between the two methods of measurements, and that approaching infinity or negative infinity denoted poor agreement. Data obtained for patients with GERD and LPR were pooled for analysis. The Bland-Altman plots were used to compare the agreement between the conventional and simple MNBI measurements, and to assess the bias. The Bland-Altman plots were constructed by plotting the mean of paired values on the X axis against the difference between paired values on the Y axis. Limits of agreement, or 95% confidence interval (CI), were obtained by calculating ± 1.96 standard deviation. A *P* value of <0.05 was considered statistically significant.

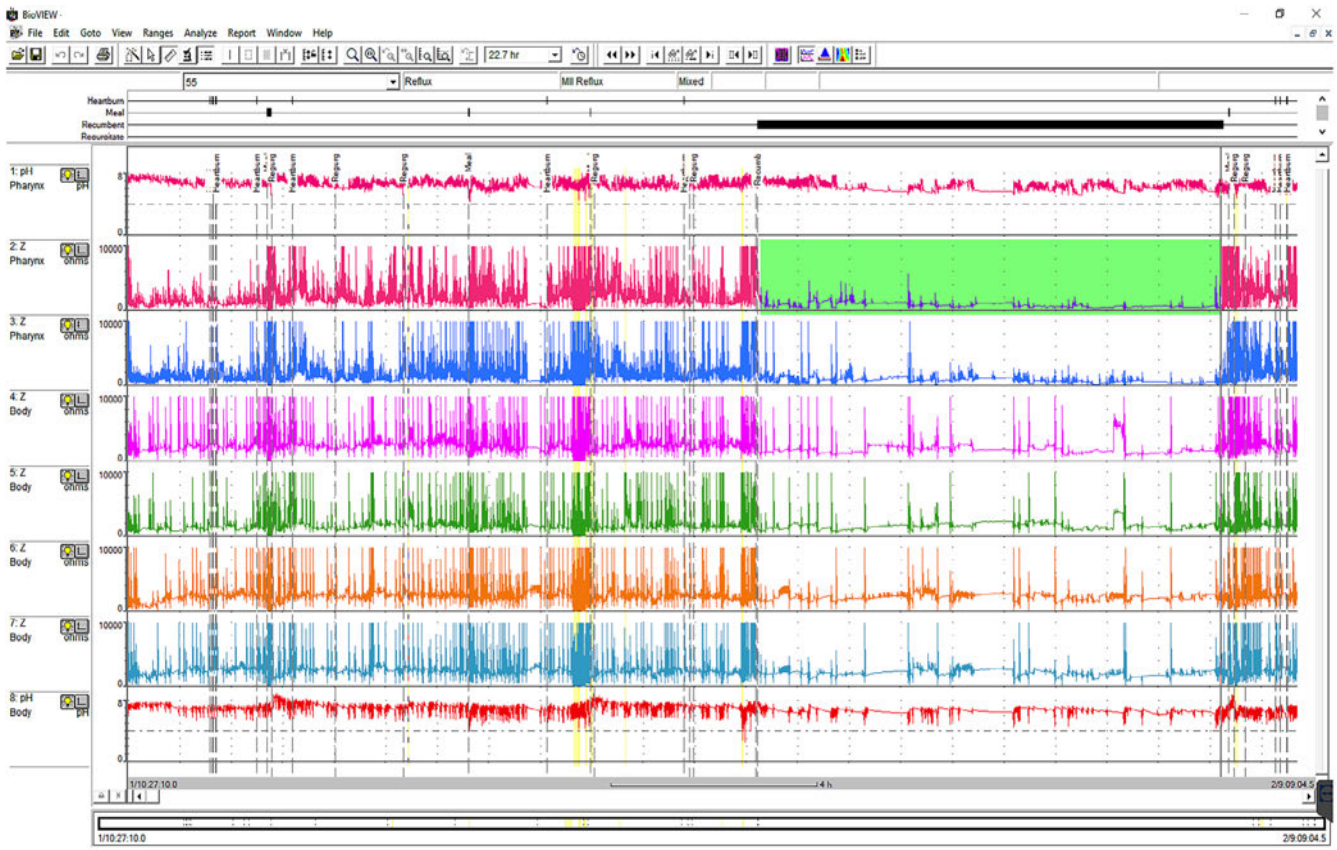


FIGURE 1 24-hour impedance-pH reflux tracing, with highlighted (green) period representing the nocturnal recumbent period [Color figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

3.1 | Demographic characteristics

In total, 187 patients were studied consecutively, including 105 with LPR and 82 with GERD. Their demographic characteristics and MII-pH measurement results are summarized in Table 1. The LPR group was elder (58.5 y ± 15.1 y vs 50.7 y ± 16.2 y, $P = 0.002$) and included a less proportion of men (29.5% vs 43.9%, $P = 0.047$) than the GERD group. The GERD group had a higher DeMeester score (12.1 ± 28.1 vs 5.5 ± 13.6, $P = 0.037$), higher distal AET (8.3% ± 7.9% vs 1.7% ± 3.9%, $P < 0.001$) and more frequent reflux episodes in the distal (64.4 ± 39.0 vs 46.5 ± 24.5, $P < 0.001$) and proximal esophagus (33.6 ± 26.8 vs 24.3 ± 14.2, $P = 0.003$). Using the conventional MNBI measurement, patients in the GERD group had a lower MNBI in the distal ([1679 ± 914] Ω vs [2109 ± 863] Ω, $P = 0.001$) and proximal esophagus ([2289 ± 579] Ω vs [2541 ± 471] Ω, $P = 0.001$) than patients with LPR. The pharyngeal MNBI measurements between the groups were similar.

3.2 | Comparison between conventional and simple MNBI

The differences between each pair of values of the conventional and simple MNBI were evaluated for the three anatomical locations. The mean difference was (−89 ± 328) Ω in the distal esophagus, (−6 ± 653) Ω in the proximal esophagus, and (128 ± 577) Ω in the pharynx, respectively. The Bland-Altman plots were constructed separately for the distal esophagus (Figure 2), proximal esophagus (Figure 3) and pharynx (Figure 4), respectively.

A strong positive correlation of MNBI values was found in the conventional and simple measurement methods. For the two measurement methods, the coefficient was 0.940 in the distal esophagus, 0.463 in the proximal esophagus and 0.712 in the pharynx (all $P < 0.001$; Table 2). The MNBI in the distal esophagus measured by using the conventional and simple measurement methods was inversely correlated with distal AET ($r = -0.195$, $P = 0.007$; and $r = -0.220$, $P = 0.003$, respectively). Both conventional and simple MNBI in the distal esophagus were inversely correlated with the number of distal acid reflux episodes ($r = -0.330$, $P < 0.001$; and $r = -0.302$, $P < 0.001$, respectively).

4 | DISCUSSION

Persistent esophageal acid exposure in both the animal model[6] and human[7] has been shown to decrease baseline impedance of the esophageal mucosa. One study found significantly lower baseline impedance levels in a group of GERD patients with pathological AET compared with healthy controls.1 Furthermore, AET has been negatively correlated with distal baseline impedance.[1,2,4] MNBI is a useful

	LPR (N = 105)	GERD (N = 82)	*P* value
Age, y (mean ± SD)	58.5 ± 15.1	50.7 ± 16.2	0.002
Male gender, n (%)	31 (29.5)	36 (43.9)	0.047
DeMeester score (mean ± SD)	5.5 ± 13.6	12.1 ± 28.1	0.037
Distal AET, % (mean ± SD)	1.7 ± 3.9	8.3 ± 7.9	<0.001
Proximal AET, % (mean ± SD)	0.2 ± 1.3	0.4 ± 3.2	0.591
Distal reflux episodes, n (mean ± SD)	46.5 ± 24.5	64.4 ± 39.0	<0.001
Acidic	12.6 ± 14.8	17.2 ± 17.3	0.011
Non-acidic	33.4 ± 18.3	44.4 ± 36.5	0.067
Proximal reflux episodes, n (mean ± SD)	24.3 ± 14.2	33.6 ± 26.8	0.003
Acidic	6.6 ± 8.5	9.9 ± 9.9	0.015
Non-acidic	17.6 ± 11.8	24.0 ± 26.0	0.028
Pharyngeal reflux episodes, n (mean ± SD)	7.4 ± 7.2	6.9 ± 7.8	0.683
Acidic	0.21 ± 1.3	0.22 ± 1.3	0.959
Non-acidic	7.2 ± 7.0	6.8 ± 7.6	0.725
Conventional MNBI, Ω (mean ± SD)			
Distal esophagus	2109 ± 863	1679 ± 914	0.001
Proximal esophagus	2541 ± 471	2289 ± 579	0.001
Pharynx	2116 ± 699	2133 ± 770	0.878

TABLE 1 Demographic characteristics and multichannel intraluminal impedance-pH measurement results of patients with gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux (LPR)

Abbreviations: AET, acid exposure time; MNBI, mean nocturnal baseline impedance; SD, standard deviation.

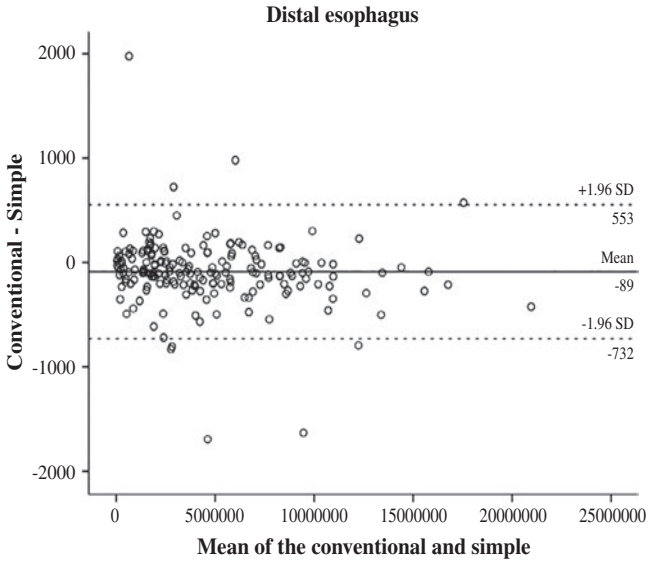


FIGURE 2 Bland-Altman plot for conventional and simple mean nocturnal baseline impedance measurement in the distal esophagus (n = 187). Abbreviation: SD, standard deviation

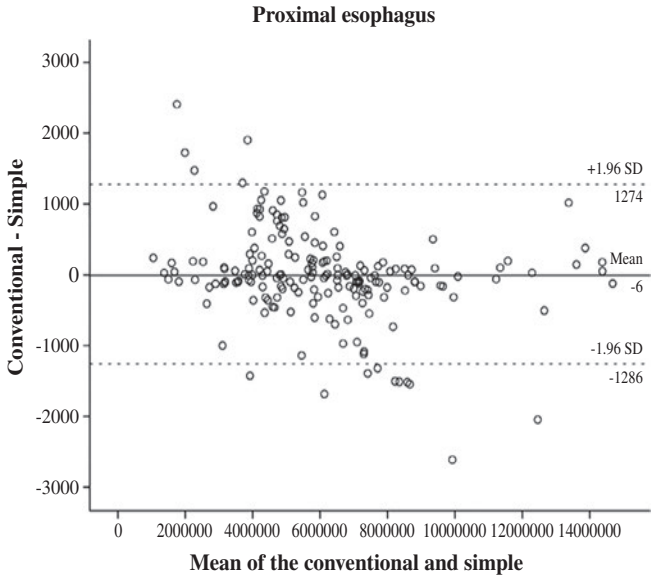


FIGURE 3 Bland-Altman plot for conventional and simple mean nocturnal baseline impedance measurement in the proximal esophagus (n = 187). Abbreviation: SD, standard deviation

novel measurement with potential utility in enhancing the diagnostic ability of MII-pH monitoring.

The present study found excellent agreement between the conventional and simple methods for the measurement of MNBI. According to the mean difference, on average, the two methods differed in measurement in the distal esophagus by 89 Ω (towards the simple method), in the proximal esophagus by 6 Ω (towards the simple method), and in the pharynx by 128 Ω (towards the conventional method). Average values for MNBI by either method are measured in the thousands; therefore, the scale of difference between both measurement methods is very low.

The distribution of points along the Bland-Altman plots for the distal and proximal esophagus are uniformly scattered. This suggests minimal bias when measuring MNBI by either the conventional or simple methods at these two sites. However, in the pharynx the distribution of the values on the plot appears to be slightly weighted

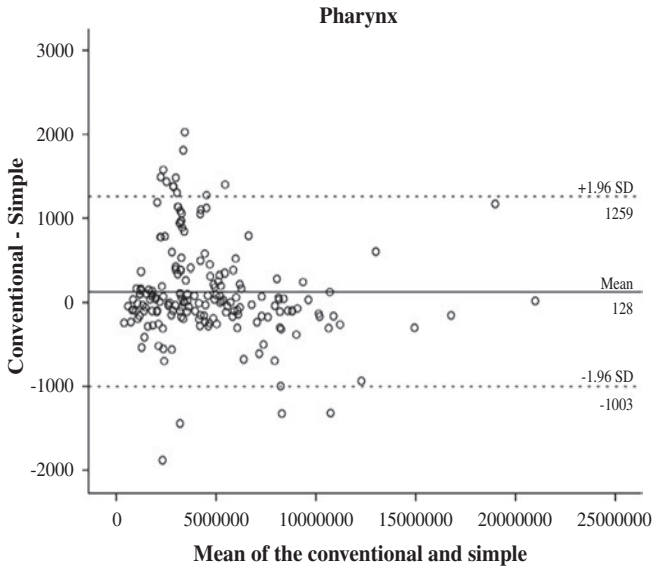


FIGURE 4 Bland-Altman plot for conventional and simple mean nocturnal baseline impedance measurement in the pharynx (n = 187). Abbreviation: SD, standard deviation

TABLE 2 Correlation and absolute values of mean nocturnal baseline impedance by the conventional and simple measurement methods

	Conventional	Simple	*r*	*P* value
Distal esophagus	1921 ± 909	2011 ± 958	0.940	<0.001
Proximal esophagus	2431 ± 534	2437 ± 697	0.463	<0.001
Pharynx	2124 ± 729	1996 ± 785	0.712	<0.001

Note: Units of measurement in Ω, values presented as mean ± standard deviation.

towards being negative. This suggests that the simple method modestly overestimate MNBI relative to the conventional method. None of the three plots appear to have a linear gradient, indicating that there is minimal proportional bias between the two methods of measurement.[8]

The correlation between the conventional and simple methods is excellent in the distal esophagus and moderate in the proximal esophagus and pharynx. One study reported a strong correlation between the conventional and simple methods in the distal and proximal esophagus, which is analogous to the anatomic locations in the current study, with correlation coefficients of 0.95 and 0.80, respectively. These authors did not measure pharyngeal MNBI. Their reported correlation coefficients in the distal esophagus are comparable to our results. However, the present study did not find the correlation to be as strong in the proximal esophagus as in this study.

The Spearman's correlation test was used in one study[5] to compare the two MNBI measurement methods. This test assesses the relationship between two variables, not the difference, and so lacks the ability to detect bias in method comparison studies, particularly proportional and fixed bias.[9,10]

The present study finds that MNBI measured by the conventional and simple methods in the distal esophagus are inversely correlated with distal AET and distal acid reflux episodes. Multiple studies have found MNBI to inversely correlate with AET, which strongly suggests that acid exposure in the distal esophagus decreases baseline impedance.[2,4,11] Currently, acid reflux is thought to induce changes in mucosal intercellular tight junctions, leading to dilated intercellular spaces, which has been shown in animal models and human studies to be induced by acid exposure and may be the cause of the decrease in electrical impedance of mucosal tissue that has impaired integrity.[6,7]

The present study is limited by its retrospective nature. Additionally, we did not compare interobserver agreement between the two methods of MNBI measurement.

5 | CONCLUSIONS

The present study demonstrates excellent agreement between conventional and simple methods of measuring MNBI. There is no evidence of proportional bias in either measurement method. MNBI results obtained by the two methods correlated excellently in the distal esophagus and moderately well in the proximal esophagus and pharynx. This study supports the use of the simple method of measuring MNBI, which allows the easy application of a useful technique in diagnosing esophageal disease, with the potential to enhance the diagnosis of reflux disease.

ORCID

Jin-soo Park https://orcid.org/0000-0003-0888-1204

REFERENCES

1. Kessing BF, Bredenoord AJ, Weijenborg PW, Hemmink GJM, Loots CM, Smout AJPM. Esophageal acid exposure decreases intraluminal baseline impedance levels. *Am J Gastroenterol*. 2011;106(12):2093-2097.
2. Martinucci I, de Bortoli N, Savarino E, et al. Esophageal baseline impedance levels in patients with pathophysiological characteristics of functional heartburn. *Neurogastroenterol Motil*. 2014;26(4):546-555.
3. Frazzoni M, Savarino E, de Bortoli N, et al. Analyses of the post-reflux swallow-induced peristaltic wave index and nocturnal baseline impedance parameters increase the diagnostic yield of impedance-pH monitoring of patients with reflux disease. *Clin Gastroenterol Hepatol*. 2016;14(1):40-46.
4. Patel A, Wang D, Sainani N, Sayuk GS, Gyawali CP. Distal mean nocturnal baseline impedance on pH-impedance monitoring predicts reflux burden and symptomatic outcome in gastro-esophageal reflux disease. *Aliment Pharmacol Ther*. 2016;44(8):890-898.
5. Hoshikawa Y, Sawada A, Sonmez S, et al. Measurement of esophageal nocturnal baseline impedance: a simplified method. *J Neurogastroenterol Motil*. 2020;26(2):241-247.
6. Farré R, Blondeau K, Clement D, et al. Evaluation of oesophageal mucosa integrity by the intraluminal impedance technique. *Gut*. 2011;60(7):885-892.

7. Farré R, van Malenstein H, De Vos R, et al. Short exposure of oesophageal mucosa to bile acids, both in acidic and weakly acidic conditions, can impair mucosal integrity and provoke dilated intercellular spaces. *Gut*. 2008;57(10):1366-1374.
8. Altman DG, Bland JM. Measurement in medicine: the analysis of method comparison studies. *J Roy Stat Soc Ser D (The Statistician)*. 1983;32(3):307-317.
9. Ludbrook J. Statistical techniques for comparing measurers and methods of measurement: a critical review. *Clin Exp Pharmacol Physiol*. 2002;29(7):527-536.
10. Giavarina D. Understanding Bland Altman analysis. *Biochem Med (Zagreb)*. 2015;25(2):141-151.
11. Sakin YS, Vardar R, Sezgin B, et al. The diagnostic value of 24-hour ambulatory intraesophageal pH-impedance in patients with laryngopharyngeal reflux symptoms comparable with typical symptoms. *United Eur Gastroenterol J*. 2017;5(5):632-640.

How to cite this article: Park J, Van der Wall H, Falk GL. Conventional and simple methods of measuring esophageal nocturnal baseline impedance show excellent agreement. *J Dig Dis*. 2021;22(7):419–424. https://doi.org/10.1111/1751-2980.13024

European Archives of Oto-Rhino-Laryngology
https://doi.org/10.1007/s00405-021-06658-z

LARYNGOLOGY

A new diagnostic paradigm for laryngopharyngeal reflux disease: correlation of impedance-pH monitoring and digital reflux scintigraphy results

Jin-soo Park[1,2] · Oleksandr Khoma[1,2] · Leticia Burton[2,3] · Hans Van der Wall[2,3] · Gregory Leighton Falk[1,4]

Received: 29 October 2020 / Accepted: 28 January 2021

Abstract

Purpose No gold-standard investigation exists for laryngopharyngeal reflux (LPR). Multichannel intraluminal impedance (MII)-pH testing has uncertain utility in LPR. Meanwhile, reflux scintigraphy allows immediate and delayed visualisation of tracer reflux in the esophagus, pharynx, and lungs. The present study aimed to correlate MII-pH and scintigraphic reflux results in patients with primary LPR.

Methods Consecutive patients with LPR underwent MII-pH and scintigraphic reflux studies. Abnormal values for MII-pH results were defined from existing literature. MII-pH and scintigraphic data were correlated.

Results 105 patients with LPR [31 males (29.5%), median age 60 years (range 20–87)] were studied. Immediate scintigraphic reflux was seen in the pharynx in 94 (90.4%), and in the proximal esophagus in 94 (90.4%). Delayed scintigraphic contamination of the pharynx was seen in 101 patients (96.2%) and in the lungs of 56 patients (53.3%). For MII-pH, abnormally frequent reflux was seen in the distal esophagus in 12.4%, proximal esophagus in 25.7%, and in the pharynx in 82.9%. Patients with poor scintigraphic clearance had higher Demeester scores ($p = 0.043$), more proximal reflux episodes ($p = 0.046$), more distal acid reflux episodes ($p = 0.023$), and more prolonged bolus clearance times ($p = 0.002$).

Conclusion Reflux scintigraphy has a high yield in LPR patients. Scintigraphic time-activity curves correlated with validated MII-pH results. A high rate of pulmonary microaspiration was found in LPR patients. This study demonstrated a high level of pharyngeal contamination by scintigraphy and MII-pH, which supports the use of digital reflux scintigraphy in diagnosing LPR.

Keywords Pharyngeal impedance · Laryngopharyngeal reflux · Pulmonary microaspiration

Introduction

Laryngopharyngeal reflux (LPR) refers to the symptoms that are a direct and indirect effect of refluxed gastric contents in the larynx and pharynx. Although typical gastroesophageal reflux disease (GERD) is well documented and investigated, extra-esophageal manifestations of GERD are less understood. LPR is associated with atypical symptoms such as chronic cough, hoarseness, dysphonia, and globus. As few as three episodes of intermittent reflux per week can result in laryngeal damage [1]. Aspirated gastric refluxate is also associated with lower respiratory sequalae such as asthma and pulmonary fibrosis [2]. LPR and GERD have dissimilar physiological mechanisms, response to treatment, and symptoms. Furthermore, LPR and GERD symptoms do not correlate, as less than 50% of patients with LPR symptoms have typical GERD symptoms [3], and only 32.8% of patients with proven GERD have extra-esophageal manifestations [4]. Nonetheless, LPR is classified in the Montreal consensus as a reflux phenomenon [5].

The current gold standard for investigating typical esophageal GERD is with multichannel intraluminal impedance combined with pH monitoring [6]. Electrical impedance across two electrodes is measured at multiple points along an esophageal

✉ Jin-soo Park
jinsoopark91@gmail.com

1 Department of Surgery, Concord Repatriation General Hospital, Sydney, NSW, Australia

2 School of Medicine, University of Notre Dame, Sydney, NSW, Australia

3 CNI Meadowbank, Sydney, NSW, Australia

4 University of Sydney, Sydney, NSW, Australia

Published online: 13 February 2021

catheter. Electrolyte-rich fluid causes a decrease in impedance, allowing quantification as well as analysis of bolus movement patterns. For each reflux episode, a pH monitor simultaneously measures the acidity of the bolus, thereby classifying reflux events as acid or non-acid. Nonetheless, 24-h pH monitoring has limitations, being negative in up to 34% of patients with reflux esophagitis [7].

Although impedance-pH monitoring is useful in investigating typical GERD, various limitations in assessing LPR have been identified. Typical impedance-pH probes cannot directly measure impedance in the pharynx, larynx, and the lungs, as conventional GERD-detecting probes lack reliability above the upper esophageal sphincter (UES). Reports in the literature use measurements in the proximal esophagus as a surrogate for refluxate reaching areas above the UES, which is imprecise [8]. There are limited standardized results for the proximal-most sensor (be it pharyngeal or upper esophageal), and there are heterogenous diagnostic criteria to define LPR in impedance-pH [3]. Inaccuracies in impedance and pH measurement also result from loss of mucosal contact or drying of the electrodes, resulting in "pseudo-reflux" artifact [9]. Inter-observer error in interpreting results for reflux events in the pharynx has also been problematic [10].

A new digital reflux scintigraphy technique has been developed which has the potential to directly visualise reflux occurring, and to certain anatomic levels. Radio-labelled technetium-99 m (Tc-99 m) phytate is ingested, and its presence in gastric refluxate can be directly visualized in the pharynx, sinuses, and lungs independent of artefact, pH, or surrogate interpretation. Concentration over time in regions of interest can be traced and quantified in real time. It also enables synchronous diagnosis of pulmonary aspiration and delayed liquid gastric emptying. This technique has been validated and reported, and is a reliable technique for detection of suspected LPR events [10, 11]. We have previously shown that no healthy, asymptomatic volunteers had pharyngeal reflux or lung aspiration with reflux scintigraphy [13].

The aim of this study was to assess two modes of investigations, impedance-pH monitoring and digital reflux scintigraphy, in consecutive patients with symptoms of laryngopharyngeal reflux. The authors hypothesize that reflux scintigraphy would complement investigation of reflux above the upper esophageal sphincter, possibly better characterizing LPR.

Methods

Patient selection and data collection

Consecutive patients between June 2013 and April 2016 with predominantly laryngopharyngeal reflux (LPR) symptoms were referred to a tertiary anti-reflux surgical service. Patients underwent standardised symptom-based interviews to characterize GERD and LPR symptoms. Patients had previously undergone extensive investigation by multiple specialties to exclude alternative diagnoses, as well as to characterize associated findings such as hiatus hernia. As patients were referred from multiple different subspecialty groups, laryngoscopic examination was not performed in all patients and was not included. The validity and reliability of laryngoscopic diagnosis of LPR was also a concern [14]. All were referred with intractable symptoms for consideration of surgery. Patients were considered to have a high pre-testing probability of disease due to extensive pre-referral treatment and investigations.

24-h ambulatory multichannel intraluminal impedance-pH monitoring and scintigraphic reflux studies were obtained in all patients while off proton-pump inhibitor (PPI) therapy for a minimum of 48 h.

Impedance-pH measurement

Standard water perfused manometry using a Dentsleeve (Ontario, Canada) multi-channel catheter was performed. The locations of the upper and lower esophageal sphincters were manometrically quantified by distance from nares, allowing precise placement of impedance-pH probes.

24 h impedance-pH measurement was performed after cessation of anti-acid therapy for 48 h. Under topical anaesthetic, a 2.3 mm diameter trans-nasal catheter designed for detection of LPR was inserted. The pharyngeal sensor was placed 2 cm above the upper border of the upper esophageal sphincter (UES), and multiple impedance sensors were subsequently close to 5 and 15 cm above the lower esophageal sphincter (LES) (Zephyr device ZAI-BL-56, Sandhill Co, Highlands Ranch, CO, USA). There were no dietary restrictions during the monitoring period other than restricting ingestion of acidic beverages. The catheter was connected to an external Zephyr device for monitoring. Impedance and pH values for reflux episodes were computer-generated using the 'Autoscan' function, and all reflux episodes were manually reviewed to confirm pharyngeal and esophageal reflux events.

Impedance-pH interpretation

A reflux episode was defined as a 50% decrease in impedance from baseline in the distal impedance sites travelling in a retrograde fashion. Whether a reflux episode was categorised as distal esophageal, proximal esophageal, or pharyngeal depended on the uppermost electrode that detected the reflux bolus transit. For example, a pharyngeal reflux episode began as a distal bolus that travelled in a retrograde fashion and was detected above the UES, congruent with other described pharyngeal reflux studies [15]. The number of reflux episodes to the pharynx, proximal esophagus, and

distal esophagus were measured while upright, recumbent, and total. Each reflux episode was classified as either an acid (pH < 4) or non-acid (pH ≥ 4) episode.

Normal values in healthy, asymptomatic individuals have been reported by Shay and colleagues for the number of reflux episodes in the proximal and distal esophagus whist upright, recumbent, and total [16]. Values above the 95th percentile in normal patients were considered abnormal. The number of reflux episodes detected at the proximal esophagus greater than 29, 3, and 31, while upright, recumbent, and total, respectively, were considered abnormal. The number of reflux episodes in the distal esophagus greater than 67, 7, and 73, while upright, recumbent, and total, respectively, were considered abnormal. Hoppo and colleagues describe normative pharyngeal impedance-pH data in healthy, asymptomatic individuals—one or more reflux episodes detected at the pharynx was considered abnormal [15], a cut-off value agreed upon by Zerbib et al. [9]

Acid exposure time (AET, %) was defined as total length of time that pH was < 4, divided by the total time monitored, and expressed as a percentage. AET was measured in the proximal and distal esophagus while upright, recumbent, and total. AET in the distal esophagus while upright, recumbent, and total, that were greater than 9.7, 2.1, and 6.3%, respectively, were considered abnormal [16].

For each reflux episode, bolus entry was defined as the moment when a 50% fall in impedance from baseline impedance was reached. Bolus clearance was defined as the moment when impedance rose back to the value denoting bolus entry for ≥ 5 s. Bolus clearance time was the time between bolus entry and clearance. Median bolus clearance time (MBCT) was calculated for each patient and expressed in seconds. MBCT was measured while upright, recumbent, and total. MBCT that were greater than 43, 51, and 44 s while upright, recumbent, and total, respectively, were considered abnormal [16].

The well-established composite score for standard distal pH reflux disease described by Johnson and Demeester was recorded. A Demeester score > 14.72 was considered abnormal [17].

Reflux scintigraphy measurement

The standardized protocol for novel digital reflux scintigraphy has been previously described [18]. Patients were fasted for 12 h and medications ceased 24 h prior to reflux scintigraphy. While upright, participants stood in front of a Hawkeye-4 gamma camera (General Electric, Milwaukee, USA) with markers over the chin and stomach to capture regions of interest in the study field. Patients ingested 50 mL of water with 60 MBq of Tc-99 m phytate, followed by another 50 mL of water to flush the pharynx and esophagus of Tc-99 m phytate. Early, dynamic images of the upright laryngopharynx, esophagus, and stomach were obtained for two minutes at one frame per 15 s. Patients lied down afterwards, and dynamic images were obtained for 30 min at one frame per 30 s. These upright and supine images detected early reflux of tracer to the esophagus and laryngopharynx. Delayed images were acquired two hours after ingestion of Tc-99 m phytate to assess isotope contamination of the laryngopharynx (Fig. 1) and lungs.

Reflux scintigraphy interpretation

Scintigraphic counts were obtained in the pharynx and upper esophagus. Scintigraphic counts were quantified over time and expressed as a time-activity curve for each location, while upright and supine. Scintigraphic time-activity curves were classified according to whether they demonstrated a falling curve, flat curve, or rising curve (Fig. 2). Patients were also grouped according to whether they exhibited a flat or rising curve, which indicated impaired ability either to clear the pharynx or esophagus of isotope, or continued accumulation. The other grouping was of a falling curve or no reflux, which indicated that patients could clear the isotope or had no net accumulation of reflux of isotope.

Using the time-activity curve, frequency of reflux spikes, maximal amplitude, and area under the curve (AUC) of scintigraphic count relative to background radiation were obtained. The amplitude reflected the volume of the bolus of refluxate that entered the pharynx and the frequency quantified the number of reflux boluses in the study period. The AUC reflected the dynamic equilibrium of volume and frequency of refluxate and the effectiveness of esophageal clearance mechanisms.

Ethical consideration

Consecutive data were extracted from a research database of either proven or suspected GERD/LPR pathology which had been approved by the Institutional Ethics Committee of Concord Hospital (LNR/12CRGH/248). Patients gave written

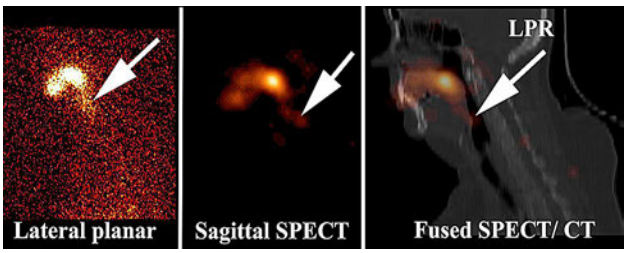


Fig. 1 This panel of images demonstrates a planar lateral image and the sagittal SPECT and fused SPECT/CT images. The main finding is of refluxate contaminating the oropharynx, pharynx and the laryngopharynx (arrow)

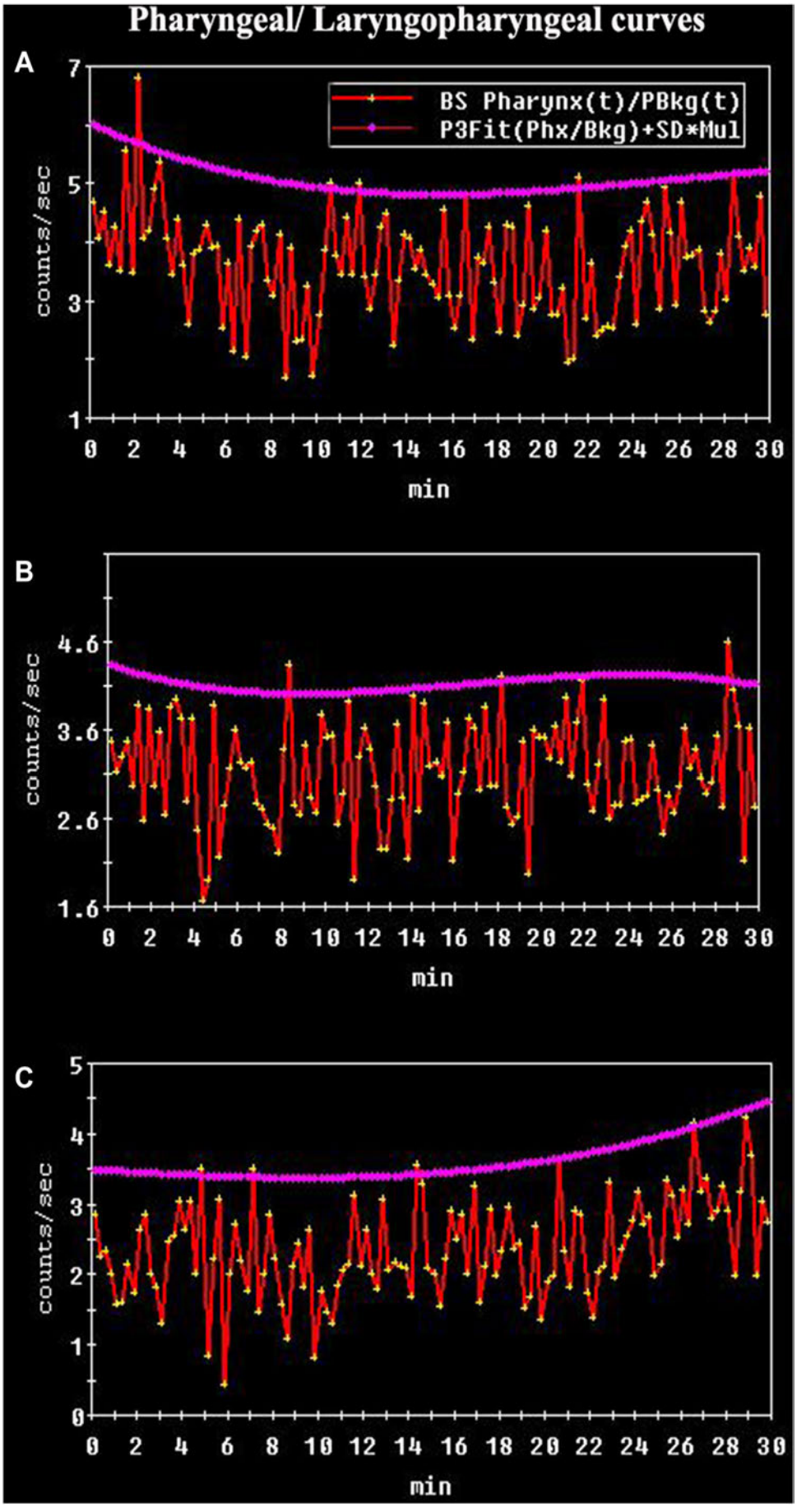


Fig. 2 This image demonstrates an example of time-activity curves derived from the region of interest over the pharynx/laryngopharynx. **a** Demonstrates a declining time-activity curve with the pink line fitted to the background subtracted raw data (Red curve). **b** shows a flat curve and **c** a rising curve

informed consent for the study under the Institutional Ethics Committee Guidelines.

Statistical analysis

SPSS version 24.0 (IBM Corp, NY) was used for statistical analysis. Data were confirmed to be non-normally distributed with Shapiro–Wilk test. Data were expressed as medians and interquartile range (25th and 75th), unless indicated. Proportions of nominal and ordinal data were compared with chi-squared test. Non-parametric continuous variables were compared with the Mann–Whitney *U* test for two variables, or Kruskal–Wallis test for more than two variables. Correlations between two continuous variables were assessed with Spearman's rank correlation, and expressed as Spearman's rho. The threshold for significance was $p < 0.05$.

Results

Clinical

105 consecutive patients were identified with predominant symptoms of laryngopharyngeal reflux (LPR). There were 31 males (29.5%) with a median age of 60 (range 20–87). The most common symptom was cough in 79 (75.2%), followed by throat clearing in 77 (73.3%) and dysphonia in 68 (64.8%). A history of typical symptoms of gastro-esophageal reflux disease (heartburn) was elicited in three (2.9%) patients. Demographics are summarized in Table 1.

Table 1 Patient demographics and clinical findings

Male sex	
Male	31 (29.5%)
Female	74 (71.5%)
Age (median, range)	60 (20–87)
Symptoms[a]—LPR	
Cough	79 (75.2%)
Throat clearing	77 (73.3%)
Dysphonia	68 (64.8%)
Mucous	64 (61%)
Globus	63 (60%)
Regurgitation to throat	57 (54.3%)
Sore throat	53 (50.5%)
Dysphagia	41 (39%)
Dyspnoea	35 (33.3%)
Non-viral bronchitis	20 (19%)
Laryngospasm	19 (18.1%)
Symptoms[a]—typical	3/105 (2.9%)

[a]Symptoms have been assessed with standardised questionnaire

Reflux scintigraphy results

Scintigraphic time-activity curve data was unavailable for one patient, whose results were uninterpretable for technical reasons, and the test was not repeated.

Scintigraphic time-activity curve findings in the pharynx

Early scintigraphic reflux findings are shown in Table 2. While upright, early scintigraphic pharyngeal reflux was seen in 94 patients (90.4%), and no pharyngeal reflux in 10 (9.6%). In those with pharyngeal reflux, scintigraphic isotope curves were rising in 50 (48.1%), flat in 14 (13.5%), and falling in 30 (28.8%).

While supine, early scintigraphic pharyngeal reflux was seen in 94 patients (90.4%), and no reflux in 10 (9.6%). In those with pharyngeal reflux, scintigraphic isotope curves were rising in 68 (65.4%), flat in 3 (2.9%), and falling in 23 (22.1%).

Table 2 Immediate scintigraphic reflux results

	$N = 104$
Pharynx while upright	
No reflux	10 (9.6%)
Falling curve	30 (28.8%)
Flat curve	14 (13.5%)
Rising curve	50 (48.1%)
Pharynx while supine	
No reflux	10 (9.6%)
Falling curve	23 (22.1%)
Flat curve	3 (2.9%)
Rising curve	68 (65.4%)
Proximal esophagus while upright	
No reflux	10 (9.6%)
Falling curve	48 (46.2%)
Flat curve	9 (8.7%)
Rising curve	37 (35.6%)
Proximal esophagus while supine	
No reflux	9 (8.7%)
Falling curve	45 (43.3%)
Flat curve	12 (11.5%)
Rising curve	38 (36.5%)

Scintigraphic time-activity curve findings in the proximal esophagus

While upright, early scintigraphic proximal esophageal reflux was seen in 94 patients (90.4%), and no proximal esophageal reflux in 10 (9.6%). In those with proximal

esophageal reflux, scintigraphic isotope curves were rising in 37 (35.6%), flat in 9 (8.7%), falling in 48 (46.2%).

While recumbent, early scintigraphic proximal esophageal reflux was seen in 95 patients (91.3%), and no proximal esophageal reflux in 9 (8.7%). In those with reflux, scintigraphic isotope curves were rising in 38 (36.5%), flat in 12 (11.5%), and falling in 45 (43.3%).

Delayed phase scintigraphic findings

Images obtained two hours after ingestion of tracer demonstrated delayed contamination of the pharynx in 101 patients (96.2%) and delayed contamination of the lungs in 56 patients (53.3%).

Two patients did not have any evidence of reflux of scintigraphic isotope in the pharynx or proximal esophagus in any position and had no pulmonary aspiration.

The median frequency of pharyngeal and upper esophageal reflux episodes above 1.5 times background radiation was 16 (range 0–43). The median maximum amplitude was 1.8 counts/second (range 0–8). Median area under the time-isotope curve (AUC) was 0.9 (range 0–3.4).

Impedance-pH results

Results of 24-h ambulatory impedance-pH monitoring were available for all 105 patients. Median Demeester score was 1.2 (range 0.8–123.3). Nine patients (8.6%) had an abnormal Demeester score (> 14.72).

Distal esophageal impedance-pH findings

Distal esophageal impedance-pH findings are summarized in Table 3. In the distal esophagus, median acid exposure time (AET, %) was normal while upright, recumbent, and in both positions. Abnormally long AET while upright (> 9.7%) was seen in 4 (4.1%) patients, abnormal AET, while recumbent (> 2.1%) was seen in 10 (10.2%) patients, and abnormal total AET (> 6.3%) was seen in 4 (4.1%) patients.

In the distal esophagus, the median number of all reflux episodes was normal while upright, recumbent, and in both positions. An abnormally high amount of total reflux episodes while upright (> 67 episodes) was seen in 9 (9.1%) patients. Median bolus clearance time (MBCT) was calculated for each patient, and the study group median was normal in all positions. Prolonged, or abnormal, MBCT, while upright (> 43 s) was seen in 1 (1%) patient, while recumbent (> 51 s) was seen in 6 (5.7%) patients, and in both positions (> 44 s) was seen in 1 (1%) patient.

Proximal esophageal impedance-pH findings

Proximal esophageal impedance-pH findings are detailed in Table 4. In the proximal esophagus, median AET for the study group while upright, recumbent, and in both positions was zero. In the proximal esophagus, the median number of reflux episodes when upright was 18 (25th and 75th quartiles: 12, 29), when recumbent was 1 (25th and 75th quartiles: 0, 4.5), and in both positions was 23 (25th and 75th quartiles: 14, 32).

An abnormally high number of total reflux episodes in the proximal esophagus when upright (> 29 episodes) was seen in 25 (23.8%), when recumbent (> 3 episodes) was seen in 30 (28.6%), and in both positions (> 31 episodes) was seen in 27 (25.7%).

Pharyngeal impedance-pH findings

Pharyngeal impedance-pH findings are detailed in Table 5. In the pharynx, the median number of acid refluxes was zero in both positions. Median number of non-acid reflux episodes when upright was 0, when recumbent was 4, and total was 5. An abnormal number of pharyngeal reflux episodes was seen in 87 (82.9%) patients.

Table 3 MII-pH results at the distal esophagus

	Upright	Supine	Total (upright + supine)
AET (%)	0.35 (0, 1.925)	0 (0, 0.025)	0 (0.3, 1.55)
Abnormal[a]	4/98 (4.1%)	10/98 (10.2%)	4/98 (4.1%)
Acid reflux episodes	5 (2, 18)	0 (0, 1)	6 (2, 22)
Non-acid reflux episodes	26 (18, 39)	3 (1, 6)	30 (20, 42)
All reflux episodes	40 (26, 50)	3 (2, 7)	45 (29.5, 58)
Abnormal[b]	9/99 (9.1%)	22/99 (22.2%)	13/105 (12.4%)
MBCT (s)	15 (11.5, 19.5)	10 (4, 18)	14 (11, 19)
Abnormal[c]	1/105 (1%)	6/105 (5.7%)	1/105 (1%)

Values expressed as: median (25th, 75th quartiles)

[a]Abnormal AET: upright (> 9.7%), recumbent (> 2.1%), total (> 6.3%)

[b]Abnormal total reflux episodes: upright (> 67), recumbent (> 7), total (> 73)

[c]Abnormal MBCT: upright (> 43), recumbent (> 51), total (> 44)

Table 4 MII-pH results at the proximal esophagus

	Upright	Supine	Total (upright + supine)
AET (s)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Acid reflux episodes	2 (0, 7.5)	0 (0, 0.5)	3 (1, 9)
Non-acid reflux episodes	13 (8, 21)	1 (0, 3)	15 (9, 23)
All reflux episodes	18 (12, 29)	1 (0, 4.5)	23 (14, 32)
Abnormal[a]	25/105 (23.8%)	30/105 (28.6%)	27/105 (25.7%)

Values expressed as: median (25th, 75th quartiles)

[a]Abnormal total reflux episodes: upright (> 29), recumbent (> 3), total (> 31)

Table 5 MII-pH results at the pharynx

	Upright	Supine	Total (upright + recumbent)
Acid reflux episodes	0 (0, 0)	0 (0, 0)	0 (0, 0)
Non-acid reflux episodes	0 (0, 2.25)	4 (1, 8)	5 (2, 10.5)
All reflux episodes	0 (0, 2.25)	4 (1, 8)	5 (2, 10.5)
Abnormal[a]			87/105 (82.9%)

Values expressed as: median (25th, 75th quartiles)

[a]Abnormal total reflux episodes (> 0)

Novel reflux scintigraphy and impedance-pH result correlations

Delayed contamination in the pharynx and lung

Patients with delayed scintigraphic contamination of the pharynx had more non-acid reflux episodes in the proximal esophagus (14, 25th and 75th quartiles: 8, 21) than those without delayed pharyngeal contamination (8, 25th and 75th quartiles 4.5, 10) ($p = 0.047$).

Delayed scintigraphic contamination of the pharynx did not correlate with other impedance-pH measurements. Specifically, delayed pharyngeal scintigraphic contamination did not correlate with impedance-detected pharyngeal reflux total episodes ($p = 0.491$), proximal reflux total episodes ($p = 0.821$), or distal reflux total episodes ($p = 0.725$). Furthermore, it did not correlate with the number of abnormal impedance-detected reflux episodes in the pharynx ($p = 0.671$), proximal esophagus ($p = 0.973$), or distal esophagus ($p = 0.435$). Delayed scintigraphic contamination of the pharynx did not correlate with total AET ($p = 0.969$).

Delayed scintigraphic contamination of the lung did not correlate with any impedance-pH measure. Specifically, it did not correlate with pharyngeal reflux episodes ($p = 0.355$), proximal esophageal reflux episodes ($p = 0.931$), or distal esophageal reflux episodes ($p = 0.750$). Delayed scintigraphic contamination of the lungs did not correlate with distal total AET ($p = 0.796$).

Pharyngeal time-activity curves

For scintigraphic time-activity curves in the pharynx, patients with a flat or rising curve were compared with patients with falling curve or no reflux. Patients with a flat or rising curve had a higher Demeester score (1.55 vs. 0.9; $p = 0.043$), more frequent proximal acid reflux episodes (3 vs. 0 episodes; $p = 0.005$), and more frequent total proximal reflux episodes (23.5 vs. 15 episodes; $p = 0.046$). Patients with a flat or rising scintigraphic curve also had more frequent distal acid reflux episodes (7.5 vs. 3 episodes; $p = 0.023$), and a higher proportion of patients exhibited an abnormally prolonged median bolus clearance time (> 43 s) ($p = 0.002$).

Proximal esophageal time-activity curves

Patients with a flat or rising scintigraphic time-activity curve in the upper esophagus had more pharyngeal reflux episodes detected on impedance-pH (8 vs. 4.5; $p = 0.034$), and a longer MBCT (17 vs. 14 s; $p = 0.041$).

Pharyngeal isotope curve measures

The maximal scintigraphic count in the pharyngeal time-activity curve correlated with the number of pharyngeal reflux episodes detected by impedance-pH (rho = 0.215; $p = 0.034$), as well as the number of pharyngeal reflux episodes detected by impedance-pH while recumbent (rho = 0.255; $p = 0.013$).

The area under the pharyngeal time-activity isotope curve (AUC) correlated with the number of pharyngeal reflux episodes detected by impedance-pH (rho = 0.260; $p = 0.011$). Pharyngeal AUC approached statistical significance in its positive correlation with AET in the proximal esophagus (rho = 0.196; $p = 0.057$).

Discussion

Symptoms of laryngopharyngeal reflux (LPR) have been reported in up to a fifth of a Western adult population [15], and is implicated in up to half of patients that present with

laryngeal or voice disorders [19]. Symptoms are non-specific and may signify many different diseases such as cough hypersensitivity syndrome, asthma, different forms of pulmonary disease, and occupational lung disease. A discriminatory test is necessary and ideally needs to be inexpensive, accurate, and assess extra-esophageal reflux disease.

The present study reports poor sensitivity of impedance-pH parameters in a group of LPR patients. A minority of the studied group had abnormal Demeester score (8.6%), AET (4.1%), distal reflux episodes (12.4%), and median bolus clearance time (1%). Also, a minority of our patients had distal esophageal reflux episodes considered abnormal while upright (9.1%), recumbent (22.2%), or total (12.4%). Only a quarter of our study group had impedance-detected reflux episodes in the proximal esophagus considered abnormal while upright (23.8%), recumbent (28.6%), or total (25.7%), despite having high rates of pharyngeal contamination on scintigraphy.

These findings suggest that normative values for impedance-pH parameters in the esophagus derived from healthy patients may not be sensitive enough to diagnose LPR. Poor correlation has been shown between laryngeal changes thought to be due to reflux and impedance-pH studies [20]. Investigations and treatment typically used for GERD may not be effective in LPR, despite presumed similar physiological mechanisms. Esophageal impedance-pH monitoring to investigate LPR has been reported in the literature, and similarly shows mixed results. For instance, Lee et al. investigated 98 LPR patients esophageal (but not pharyngeal) impedance-pH. They reported diagnostic yields of 37.8 and 49% in single- and dual-channel impedance-pH measurements, respectively [21]. Anandasabapathy et al. similarly examined impedance-pH in the proximal and distal esophagus in 21 patients with globus, and found that the symptom-associated probability (the likelihood that a patient's symptoms are related to reflux) was only 41.5% for all impedance-pH detected reflux episodes [8]. These findings suggest that impedance-pH, although useful in diagnosing typical esophageal GERD, may be less effective in diagnosing extra-esophageal manifestations of reflux, such as LPR. The expectation that abnormal reflux parameters based on studies in heartburn patients would be valid in non-heartburn patients appears fallacious.

Pharyngeal pH-impedance testing

Despite the low sensitivity of proximal and distal esophageal impedance findings in LPR, 82.9% of our cohort of LPR patients had an abnormal pharyngeal reflux episodes detected by impedance monitoring, the majority of which was supine. This may reflect the severity and purity of our cohort. Any number of pharyngeal reflux events was determined as abnormal in line with findings reported by Hoppo et al. in a series of asymptomatic patients undergoing hypopharyngeal impedance-pH testing [15]. This threshold for what is considered an abnormal number of pharyngeal reflux episodes in a healthy, asymptomatic population needs to be reinforced in further, larger studies. Zerbib et al. report that in 46 healthy, asymptomatic patients off proton pump inhibitors, a median of 0 pharyngeal reflux episodes was observed, with the 95th percentile being 3 episodes [10]. Had this higher value of what is considered an abnormal number of pharyngeal reflux episodes, the sensitivity of impedance-pH in the pharynx would be markedly reduced.

The utility of pharyngeal pH testing is currently debated. The diagnostic yield of the hypopharyngeal pH sensor alone has been reported to be 41–83% in patients with suspected LPR.[9], though a multicenter study reported a yield of 14% for hypopharyngeal pH sensor [22]. A meta-analysis of sixteen studies that assessed LPR with pharyngeal impedance-pH monitoring concluded that the pharyngeal probe gives accurate and consistent information in LPR patients when placed within 2 cm above the UES [23]. Other studies have assessed the use of pharyngeal probe, but none have compared pH measure against other investigative modalities.

Oropharyngeal pH testing alone (Dx-pH measuring system, Restech) has similarly been reported to have poor sensitivity in studies that cross-examine its sensitivity with standard impedance-pH testing [24]. Oropharyngeal pH monitoring measures only acid reflux events, with the majority of the drops in pH detected by Restech Dx-pH reported to not correlate with retrograde flow in the esophageal body [25]. This technology remains unproven, and is likely only to demonstrate a minority of reflux events as events are frequently non-acidic. Additional limitations of pharyngeal impedance-pH testing for LPR include cost, unavailability in many centres, and inconvenience to the patient [3]. Zerbib et al. have described poor inter-observer agreement for impedance-pH measurements in the pharynx [10]. Hence, impedance-pH measurements in the proximal esophagus and pharynx should be interpreted with caution in the context of LPR investigation.

Value of digital scintigraphy

In the present cohort of symptomatic LPR patients, the majority had both early (90.4%) and delayed (96.2%) evidence of scintigraphic contamination of the pharynx. The present scintigraphic technique has been validated in a cohort with severe reflux disease who had undergone fundoplication [11, 12]. The present yield is higher than that reported by Bestetti et al., who reported positive reflux scintigraphy in 67% of a cohort of patients with posterior laryngitis [26]. However, the same digital technique of scintigraphic assessment was not used. Galli and colleagues report 82.9% yield in 41 patients with LPR, but again, the technique

differed [27]. Older studies used an outdated visual reporting system, whereas the present study contained scintigraphic data which was standardised and digitally interrogated, taking account of background radiation.

Digital reflux scintigraphy has various advantages compared with catheter-based tests. The initial scintigraphic assessment takes thirty minutes, with a two hour period between assessment in the immediate and delayed phases. Each reflux scintigraphy investigation exposes the patient to under 80 micro-sieverts, less than a chest x-ray. However, reflux scintigraphy has limitations as well: the test does not concurrently measure pH and cannot distinguish between acid and non-acidic reflux. The number of reflux episodes detected is over a thirty minute window, as opposed to a 24-h period as in impedance-pH monitoring, and would not capture nocturnal recumbent reflux episodes. It does, however, assess a two hour period of erect events by the delayed study.

Pharyngeal impedance measurements were positional. Most impedance-detected pharyngeal reflux episodes were in the supine position. This may be due to the catheter lying posteriorly in the pharynx while supine and detecting dependent posterior reflux events more readily. Posterior pharyngeal contact with the impedance channel may be lost while upright, and impedance measurements may not be detected. This may explain the finding that the number of reflux episodes detected by impedance-pH in the proximal esophagus, but not the pharynx, correlated with delayed pharyngeal contamination on scintigraphy. Delayed pharyngeal scintigraphy also correlated with supine impedance-detected reflux events in the pharynx, indicating that pharyngeal supine impedance is a useful test for LPR.

Despite more than half the cohort demonstrating pulmonary contamination with refluxed isotope, no impedance-pH measurement correlated with these findings. This indicates that measurement of pharyngo-esophageal impedance and pH cannot detect microaspiration, whereas scintigraphy can detect these microaspiration events two hours after reflux to the larynx has occurred.

The correlation between flat or rising pharyngeal time-activity curves with Demeester score, proximal acid episodes, total acid reflux episodes, and distal reflux suggest good concordance between scintigraphic time-activity curves in the pharynx and upper esophagus and impedance-pH measurements. These correlations further support digital scintigraphy as a valid technique to assess pharyngeal reflux contamination.

Given that the amplitude of the scintigraphic time-activity curve is proportional to the amount of refluxed gastric content and the integral of the curve (AUC) is proportional to the product of the amount of reflux and its duration [26], it is not surprising that the number of impedance-detected reflux events in the pharynx correlated with both measures. These findings confirm the association of impedance frequency in the pharynx and AUC in the pharynx.

Conclusion

Digital reflux scintigraphy was strongly positive in a symptomatic, pure group of LPR patients, with yields in the pharynx in the early phase of 90.4% and in the delayed phase of 96.2%. Supine impedance-pH demonstrated a lower rate of positivity, with abnormal reflux detected in 82.9% at the pharynx. A high likelihood of pulmonary microaspiration was found in LPR, demonstrated by scintigraphy but not by impedance monitoring. Scintigraphic time-activity curves correlated well with existing impedance-pH measurements.

Digitally-interrogated reflux scintigraphy may offer practitioners an easily performed test for confirmation of LPR, identifying most patients with this condition when laryngoscopy has not been diagnostic. A high rate of pulmonary aspiration in LPR was identified, and is only demonstrable by this technique. Further validation of digital reflux scintigraphy is warranted.

Author contributions All authors made substantial contributions to this study, approved the version to be published, and agree to be accountable for all aspects of the work.

Funding No declarations or conflicts.

Availability of data and material (data transparency) Not applicable.

Code availability (software application or custom code) Not applicable.

Compliance with ethical standards

Conflict of interest No declarations or conflicts.

Ethics approval Ethics approval as per Sydney Local Health District (Concord Hospital) Human Research Ethics Committee, reference LNR/12/CRGH/248.

Consent to participate Patients signed informed consent regarding publishing their data.

Consent for publication All patients gave written informed consent.

References

1. Koufman JA (1991) The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal. Laryngoscope 101:1–78. https://doi.org/10.1002/lary.1991.101.s53.1

2. Khoma O, Falk SE, Burton L, Van der Wall H, Falk GL (2018) Gastro-oesophageal reflux and aspiration: does laparoscopic fundoplication significantly decrease pulmonary aspiration? Lung 196(4):491–496. https://doi.org/10.1007/s00408-018-0128-4
3. Lechien JR et al (2019) Evaluation and management of laryngopharyngeal reflux disease: state of the art review. Otolaryngol Head Neck Surg 160(5):762–782. https://doi.org/10.1177/0194599819827488
4. Jaspersen D et al (2003) Prevalence of extra-oesophageal manifestations in gastro-oesophageal reflux disease: an analysis based on the ProGERD study. Aliment Pharmacol Ther 17(12):1515–1520. https://doi.org/10.1046/j.1365-2036.2003.01606.x
5. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Global Consensus Group (2006) The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 101(8):1900–1920. https://doi.org/10.1111/j.1572-0241.2006.00630.x (**quiz 1943**)
6. Gyawali CP et al (2018) Modern diagnosis of GERD: the Lyon consensus. Gut 67(7):1351–1362. https://doi.org/10.1136/gutjnl-2017-314722
7. Dent J et al (2010) Accuracy of the diagnosis of GORD by questionnaire, physicians and a trial of proton pump inhibitor treatment: the Diamond study. Gut 59(6):714–721. https://doi.org/10.1136/gut.2009.200063
8. Anandasabapathy S, Jaffin BW (2006) Multichannel intraluminal impedance in the evaluation of patients with persistent globus on proton pump inhibitor therapy. Ann Otol Rhinol Laryngol Thousand Oaks 115(8):563–570
9. Harrell SP, Koopman J, Woosley S, Wo JM (2007) Exclusion of pH artifacts is essential for hypopharyngeal pH monitoring. Laryngoscope 117(3):470–474. https://doi.org/10.1097/MLG.0b013e31802d344c
10. Zerbib F et al (2013) Normal values of pharyngeal and esophageal 24-hour pH impedance in individuals on and off therapy and interobserver reproducibility. Clin Gastroenterol Hepatol 11(4):366–372. https://doi.org/10.1016/j.cgh.2012.10.041
11. Falk GL (2015) Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? WJG 21(12):3619. https://doi.org/10.3748/wjg.v21.i12.3619
12. Falk M, Van der Wall H, Falk GL (2015) Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms. Nucl Med Commun 36(6):625–630. https://doi.org/10.1097/MNM.0000000000000289
13. Burton L, Falk GL, Beattie J, Novakovic D, Simpson S, Van der Wall H (2020) Findings from a novel scintigraphic gastroesophageal reflux study in asymptomatic volunteers. Am J Nucl Med Mol Imaging 10(6):342–348
14. Vance D et al (2020) The validity and reliability of the reflux finding score. J Voice. https://doi.org/10.1016/j.jvoice.2020.11.008
15. Hoppo T et al (2012) How much pharyngeal exposure is 'Normal'? Normative data for laryngopharyngeal reflux events using hypopharyngeal multichannel intraluminal impedance (HMII). J Gastrointest Surg 16(1):16–25. https://doi.org/10.1007/s11605-011-1741-1
16. Shay S et al (2004) Twenty-four hour ambulatory simultaneous impedance and pH monitoring: a multicenter report of normal values from 60 healthy volunteers. Am J Gastroenterol New York 99(6):1037–1043. https://doi.org/10.1111/j.1572-0241.2004.04172.x
17. Johnson LF, Demeester TR (1974) Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. Am J Gastroenterol 62(4):325–332
18. Burton L, Falk GL, Baumgart K, Beattie J, Simpson S, Van der Wall H (2020) Esophageal clearance in laryngopharyngeal reflux disease: correlation of reflux scintigraphy and 24-hour impedance/pH in a cohort of refractory symptomatic patients. Mol Imaging Radionucl Ther 29(1):7–16. https://doi.org/10.4274/mirt.galenos.2019.30085
19. Koufman JA, Amin MR, Panetti M (2000) Prevalence of reflux in 113 consecutive patients with laryngeal and voice disorders. Otolaryngol Head Neck Surg 123(4):385–388. https://doi.org/10.1067/mhn.2000.109935
20. de Bortoli N et al (2012) How many cases of laryngopharyngeal reflux suspected by laryngoscopy are gastroesophageal reflux disease-related? World J Gastroenterol 18(32):4363–4370. https://doi.org/10.3748/wjg.v18.i32.4363
21. Lee BE et al (2010) Combined dual channel impedance/pH-metry in patients with suspected laryngopharyngeal reflux. J Neurogastroenterol Motil 16(2):157–165. https://doi.org/10.5056/jnm.2010.16.2.157
22. Vaezi MF et al (2006) Treatment of chronic posterior laryngitis with esomeprazole. Laryngoscope 116(2):254–260. https://doi.org/10.1097/01.mlg.0000192173.00498.ba
23. Merati AL, Ulualp SO (2005) Toohill, "Metaanalysis of upper probe measurements in normal subjects and patients with laryngopharyngeal reflux." Ann Otol Rhinol Laryngol 114:177–182
24. Ummarino D, Vandermeulen L, Roosens B, Urbain D, Hauser B, Vandenplas Y (2013) Gastroesophageal reflux evaluation in patients affected by chronic cough: restech versus multichannel intraluminal impedance/pH metry. Laryngoscope 123(4):980–984. https://doi.org/10.1002/lary.23738
25. Hayat JO et al (2012) Su1056 do patients with hoarseness and endoscopic signs of LPR have abnormal esophago-pharyngeal reflux? A study using simultaneous impedance-phmetry, oropharyngeal pH monitoring (restech) and pepsin measurements in saliva. Gastroenterology 142(5):S411–S412. https://doi.org/10.1016/S0016-5085(12)61556-X
26. Bestetti A, Carola F, Carnevali-Ricci P, Sambataro G, Tarolo GL (2000) 99mTc-sulfur colloid gastroesophageal scintigraphy with late lung imaging to evaluate patients with posterior laryngitis. J Nucl Med 41(10):1597–1602
27. Galli J, Volante M, Parrilla C, Rigante M, Valenza V (2005) Oropharyngoesophageal scintigraphy in the diagnostic algorithm of laryngopharyngeal reflux disease: a useful exam? Otolaryngol Head Neck Surg 132(5):717–721. https://doi.org/10.1016/j.otohns.2005.01.043

Lung
https://doi.org/10.1007/s00408-021-00432-y

GERD AND ASPIRATION

Modified Reflux Scintigraphy Detects Pulmonary Microaspiration in Severe Gastro-Esophageal and Laryngopharyngeal Reflux Disease

Jin-soo Park[1,2,5] · Leticia Burton[2,3] · Hans Van der Wall[2,3] · Gregory Leighton Falk[1,4]

Received: 29 October 2020 / Accepted: 22 February 2021

Abstract

Introduction Previously described methodologies for detecting laryngopharyngeal reflux (LPR) have limitations. Symptoms alone are non-diagnostic, and pH-impedance studies have poor sensitivity. Pulmonary micro-aspiration is under-recognised in LPR and gastro-esophageal reflux disease (GERD). The present study aimed to describe the results of a modified technique for scintigraphic reflux studies in two groups with severe reflux: those with typical reflux symptoms and those with laryngopharyngeal manifestations of reflux.

Methods A prospective database of severely symptomatic, treatment-resistant reflux patients was grouped based upon predominant symptom profile of typical GERD or LPR. All patients underwent reflux scintigraphy. Results were obtained for early scintigraphic reflux contamination of the pharynx and proximal esophagus, and delayed contamination of the pharynx and lungs after 2 h.

Results 187 patients were studied (82 GERD, 105 LPR). The LPR patients were predominantly female (70.5% vs. 56.1%; $p=0.042$) and older than the GERD group (median age 60 years vs. 55.5 years; $p=0.002$). Early scintigraphic reflux was seen at the pharynx in 89.2% (GERD 87.7%, LPR 90.4%; $p=0.133$), and at the proximal esophagus in 89.7% (GERD 88.9%, LPR 90.4%; $p=0.147$). Delayed contamination of the pharynx was seen in 95.2% (GERD 93.9%, LPR 96.2%; $p=0.468$). Delayed pulmonary aspiration was seen in 46% (GERD 36.6%, LPR 53.3%; $p=0.023$).

Conclusion Reflux scintigraphy demonstrated a high rate of reflux-related pulmonary aspiration. Contamination of the proximal esophagus and pharynx was observed frequently in both groups of severe disease. The likelihood of pulmonary aspiration and potential pulmonary disease needs to be entertained in severe GERD and LPR.

Keywords Laryngopharyngeal reflux · Impedance monitoring · Reflux scintigraphy · Aspiration · Gastro-esophageal reflux disease

Introduction

Gastro-esophageal reflux disease (GERD) refers to the proximal reflux of gastric contents into the esophagus causing troublesome symptoms, typically heartburn and regurgitation. Laryngopharyngeal reflux (LPR) is caused by reflux into the larynx and pharynx, and is associated with "atypical", extra-esophageal symptoms such as chronic cough, hoarseness, and dysphonia. The Montreal consensus considers both GERD and LPR as reflux phenomena, and report that chronic cough, microaspiration, and asthma are significantly associated with GERD [1]. Furthermore, microaspiration is associated with pulmonary fibrosis, graft rejection in lung transplantation, and recurrent lung infection [2].

Reflux events are typically investigated with multichannel intraluminal impedance (MII) and pH monitoring.

✉ Jin-soo Park
Jinsoopark91@gmail.com

[1] Department of Surgery, Concord Repatriation General Hospital, Sydney, NSW, Australia

[2] School of Medicine, University of Notre Dame, Sydney, NSW, Australia

[3] CNI Meadowbank, Sydney, NSW, Australia

[4] University of Sydney, Sydney, NSW, Australia

[5] Suite 29, 12-18 Tryon Road, Lindfield, Sydney, NSW 2070, Australia

Liquid boluses decrease the electrical impedance between electrodes along a naso-esophageal catheter, hence detecting reflux events. The pH of refluxed boluses is simultaneously measured, detecting acid and non-acid reflux event frequency over a 24-h period [3].

There is currently no optimal diagnostic method in the investigation of reflux events that occur outside of the esophagus. Standard technology used in the pharynx suffers problems of drying, loss of probe contact from pharyngeal or upper esophageal mucosa causing "pseudo-reflux" artifact [4], and poor inter-observer reproducibility in the interpretation of LPR findings on MII-pH [5]. Oropharyngeal pH testing (Restech) measures only acid events, and has been shown to be less sensitive than MII-pH and with lower symptom association probability [6].

Reflux scintigraphy is an investigation which has the potential in LPR to provide quantifiable evidence of refluxate in the esophagus, pharynx, sinuses, and lungs [7]. A modified technique of reflux scintigraphy uses technetium-99m (Tc-99m) phytate, which is not absorbed by the gut, which minimises scattered radiation that may lead to imprecise measurement. Tc-99m phytate does not have problems with high background on delayed images that are as apparent as Tc-99m DTPA. As little as 0.1 MBq of activity in the lungs can be detected by the gamma camera, increasing sensitivity of detecting microaspiration of refluxate [8]. Nuclear scintigraphy is safe and well tolerated. It allows direct visualisation of refluxed tracer in the laryngopharynx, sinuses, and lungs. The methodology and validity of the scintigraphic technique in qualitatively detecting LPR has been previously reported [8, 9]. Normative values for the current modified scintigraphic technique has demonstrated that no healthy, asymptomatic volunteers demonstrated supine reflux or pulmonary aspiration [10].

There has been no direct comparison of scintigraphic results in GERD and LPR patients. Furthermore, there are no quantitative analyses of reflux scintigraphy reported that specifically assess scintigraphic counts at the laryngopharynx and proximal esophagus in a cohort of LPR patients. The present study aimed to examine the extent of reflux distribution using a new scintigraphic reflux technique in two groups of patients with severe treatment-resistant reflux disease: those with predominantly typical GERD symptoms and those with predominantly LPR manifestations.

Methods

Patient Selection and Data Collection

A prospective database of consecutive patients with severely symptomatic, treatment-refractory GERD and LPR, who had been referred to a surgical diagnostic facility for consideration of treatment, was maintained. Patients had previously undergone multidisciplinary tertiary investigation for alternate diagnoses. Standardised symptom assessments were undertaken to characterize GERD and LPR, and individuals were assigned a predominant symptom category prior to investigation. All patients underwent ambulatory, 24-h MII-pH testing with a specialised 2.3 mm diameter trans-nasal catheter designed to detect laryngopharyngeal reflux events. (ZAI-BL-56, Zephyr device, Sandhill Co, Highlands Ranch, Colorado, USA).

Reflux Scintigraphy Technique

The present protocol for quantitative reflux scintigraphy has previously been described and validated [8, 9, 11]. Patients were fasted for 12 h and proton pump inhibitors ceased 24 h prior to reflux scintigraphy. Whilst upright, patients were positioned in front of a Hawkeye 4 gamma camera (General Electric, Milwaukee, USA) with markers placed on the mandible and overlying the stomach to ensure regions of interest were within study field.

Patients swallowed 50 mL of water with 60 MBq of Tc-99m phytate, followed by a further 50 mL of water to flush the pharynx and esophagus of isotope. Early, dynamic images of the upright laryngopharynx, esophagus, and stomach were obtained for 2 min at 15 s per frame whilst upright. Patients were positioned supine immediately afterwards, and dynamic images were obtained for 30 min at 30 s per frame. These images detected early reflux of tracer at the esophagus and laryngopharynx. Delayed images were acquired 2 h following administration of Tc-99m phytate to assess tracer contamination of the laryngopharynx (Fig. 1) and lungs.

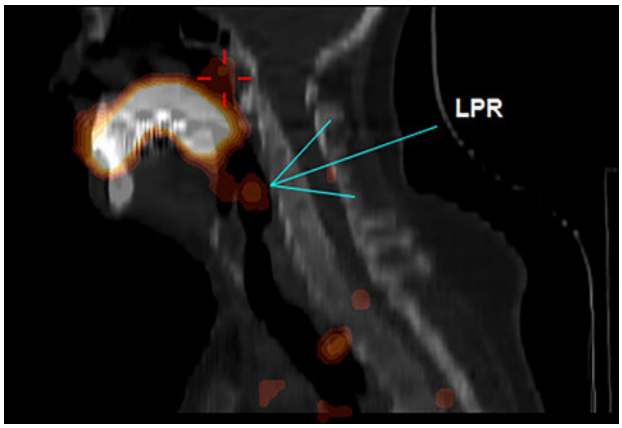


Fig. 1 Sagittal view of combined SPECT-CT demonstrating contamination of pharynx with radioactive colloid 2 h after ingestion

Reflux Scintigraphy Interpretation

Scintigraphic counts were quantified for each dynamic study using a computer-generated algorithm and graphically expressed as a separate time-activity curves for the pharynx and proximal esophagus whilst upright and supine. Time-activity curves represented early reflux activity in the pharynx and esophagus. Time-activity curves were classified as showing no reflux, a falling curve, flat curve, or rising curve (Fig. 2). This represented a dynamic balance of repeated contamination versus clearance of isotope from the pharynx or esophagus.

Area under the curve (AUC) and maximal amplitude of scintigraphic count were obtained. The amplitude reflected the volume of the bolus of refluxate that entered the pharynx and the frequency quantified the number of reflux episodes in the study period. The ratio of area under the curve to background radiation reflected the dynamic equilibrium of volume and frequency of refluxate and the effectiveness of esophageal clearance mechanisms.

Ethical Consideration

Data were extracted from a research database of patients with GERD/LPR pathology which had been approved by the Sydney Local Health District Human Research Ethics Committee (reference: LNR/12CRGH/248; approval 05/12/2012). Patients gave written informed consent for the study under the institutional ethics committee guidelines.

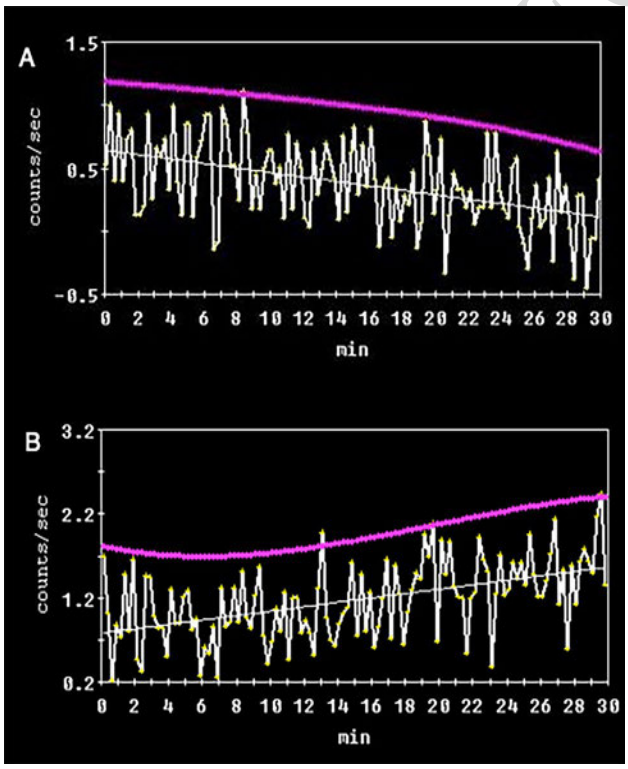


Fig. 2 Time-activity scintigraphy curves demonstrating: **a** falling curve, and **b** rising curve

Statistical Analysis

SPSS version 24.0 (IBM Corp, NY) was used for statistical analysis. Data were confirmed to be non-normally distributed with Shapiro–Wilk test. Non-parametric data were expressed as medians and ranges. Proportions of nominal and ordinal data were compared with the Chi-squared test. Non-parametric continuous variables were compared with the Mann–Whitney *U* test for two variables, or Kruskal–Wallis test for more than two variables. The threshold for significance was $p < 0.05$.

Results

Clinical

187 consecutive patients were studied, with 82 patients having GERD-predominant symptoms and 105 patients with LPR symptoms. There were 67 males (35.8%) with a median age of 58 years (range 15–87 years). All patients in the GERD group reported heartburn as the predominant symptom. Table 1 shows the symptoms described by the LPR group. The most common symptom of laryngopharyngeal reflux was cough ($n = 79$, 75.2%), followed by throat clearing ($n = 77$, 73.3%). Only three patients (2.9%) in the LPR group described a history of typical symptoms of gastroesophageal reflux disease, namely heartburn, with all three confirming that their extra-esophageal symptoms troubled

Table 1 Patient demographics and clinical findings

Male sex	67 male, 120 female
Age (Median, range)	58 (15–87)
GERD group	82
LPR group	105
LPR symptoms	
Cough	79 (75.2%)
Throat clearing	77 (73.3%)
Dysphonia	68 (64.8%)
Mucous	64 (61%)
Globus	63 (60%)
Regurgitation to throat	57 (54.3%)
Sore throat	53 (50.5%)
Dysphagia	41 (39%)
Dyspnoea	35 (33.3%)
Non-viral bronchitis	20 (19%)
Laryngospasm	19 (18.1%)

them most. In the whole cohort, five patients were aware of clinical episodes of aspiration.

In the GERD group there were 36 males (43.9%) with a median age of 55.5 years (range 15–82 years). In the LPR group there were 31 males (29.5%) with a median age of 60 years (range 20–87 years). The LPR group had a significantly higher proportion of females ($p=0.042$) and were significantly older ($p=0.002$) than the GERD group.

Reflux Scintigraphy Results

Scintigraphic time-activity curve data were unavailable for one patient, whose results were uninterpretable for technical reasons. The test was not repeated and the patient was excluded from analysis.

Scintigraphic Time-Activity Curve Findings in the Pharynx/Laryngopharynx

In the pharynx/laryngopharynx, early scintigraphic reflux was seen in 165 (89.2%) of the study population whilst upright and 166 (89.2%) whilst recumbent. Scintigraphic reflux in the pharynx/laryngopharynx between the two groups whilst upright and recumbent are described in Table 2. Whilst upright, early reflux was seen in the GERD group in 71 (87.7%) patients, and in the LPR group in 94 (90.4%) patients. Whilst recumbent, early reflux was seen in the GERD group in 72 (87.8%) patients, and in the LPR group in 94 (90.4%) patients.

In the laryngopharynx, there was no difference between GERD and LPR groups in their proportions of patients who had falling, flat, or rising curves.

Scintigraphic Time-Activity Curve Findings in the Proximal Esophagus

In the proximal esophagus whilst upright, scintigraphic reflux was seen in 166 (89.7%) of the study population whilst upright and 168 (90.8%) whilst recumbent. Scintigraphic reflux in the proximal esophagus between the two groups whilst upright and recumbent are described in Table 3. Whilst upright, early reflux was seen in the GERD group in 72 (88.9%) patients, and in 94 (90.4%) patients of the LPR group. When recumbent, the GERD group showed early reflux in 73 (89%) patients, and in the LPR group, early reflux was seen in 95 (90.5%) patients.

In the proximal esophagus, there was no difference between GERD and LPR groups in proportions of patients with falling, flat, or rising curves. Early scintigraphic findings in the proximal esophagus are shown in Table 3.

Delayed Phase Scintigraphic Findings

Delayed contamination of the laryngopharynx was seen in 178 (95.2%) of the whole group. Delayed laryngopharyngeal contamination was seen in 77 (93.9%) of the GERD group and 101 (96.2%) of the LPR group; this was not significantly different ($p=0.468$).

Radiolabelled tracer contamination of the lungs, indicating pulmonary microaspiration, was seen in 86 (46%) of the whole group on delayed studies. A significant difference was seen in pulmonary aspiration between GERD patients, 30 (36.5%) and LPR patients, 56 (53.3%) who showed pulmonary aspiration ($p=0.023$).

Table 2 Early scintigraphic findings in the pharynx

	GERD	LPR	*p* value
Upright			0.133
No reflux	10 (12.3%)	10 (9.6%)	0.636
Falling curve	21 (25.9%)	30 (28.8%)	0.741
Flat curve	6 (7.4%)	14 (13.5%)	0.236
Rising curve	44 (54.3%)	50 (48.1%)	0.459
No reflux or falling curve	31 (38.3%)	40 (38.5%)	1.000
Flat or rising curve	50 (61.7%)	64 (61.5%)	1.000
Recumbent			0.244
No reflux	10 (12.2%)	10 (9.6%)	0.573
Falling curve	18 (22%)	23 (22.1%)	0.979
Flat curve	3 (3.7%)	3 (2.9%)	0.767
Rising curve	51 (62%)	68 (65.4%)	0.653
No reflux or falling curve	28 (34.1%)	33 (31.7%)	0.728
Flat or rising curve	54 (65.9%)	71 (68.3%)	0.728

Table 3 Early scintigraphic findings in the proximal esophagus

	GERD	LPR	*p* value
Upright			0.147
No reflux	9 (11.1%)	10 (9.6%)	0.740
Falling curve	33 (40.7%)	48 (46.2%)	0.462
Flat curve	7 (8.6%)	9 (8.7%)	0.998
Rising curve	32 (40%)	37 (35.6%)	0.584
No reflux or falling curve	42 (51.9%)	58 (55.8%)	0.596
Flat or rising curve	39 (48.1%)	46 (44.2%)	0.596
Recumbent			0.362
No reflux	9 (11%)	9 (8.6%)	0.595
Falling curve	29 (35.4%)	45 (42.9%)	0.274
Flat curve	9 (11%)	12 (11.4%)	0.670
Rising curve	35 (42.7%)	38 (36.2%)	0.470
No reflux or falling curve	38 (46.3%)	54 (51.4%)	0.507
Flat or rising curve	44 (53.7%)	50 (47.6%)	0.507

Scintigraphy Curve Measures

The median frequency of pharyngeal and upper esophageal reflux episodes above 1.5 times background radiation was 16 (range 0–60) in the GERD group and 16 (range 0–43) in the LPR group; this was not significantly different ($p = 0.853$). The median maximum amplitude was 1.7 counts/second (range 0–10) in the GERD group and 1.8 (range 0–8) in the LPR group, which was not significantly different ($p = 0.624$). Median area under the time-isotope curve (AUC) was 0.8 (range 0–3.6) in the GERD group and 0.9 (range 0–3.4) in the LPR group, which was also not significantly different ($p = 0.551$).

Discussion

Symptoms of laryngopharyngeal reflux (LPR) are thought to occur through the direct effects of gastroduodenal digestive proteins such as pepsin and bile salts irritating laryngopharyngeal mucosa [12]. Asthma-like symptoms such as bronchoconstriction or cough may also be triggered by a vagally-mediated esophago-bronchial reflex when the distal esophagus is exposed to acid [13].

There is presently no generally accepted standard optimal methodology that diagnoses LPR. The Reflux Finding Score (RFS) is an eight-item severity scale based on laryngoscopic findings of laryngeal injury described by Belafsky. A score greater than seven is considered compatible with a diagnosis of LPR [14]. However, laryngoscopic findings have questionable specificity. Even within the same study described by Belafsky, age-matched control subjects without LPR had a mean RFS of 5.2. Furthermore, abnormal laryngoscopic findings have frequently been reported in asymptomatic, healthy patients in population studies [15–17]. Also, inter-observer reliability of laryngoscopic findings has been shown to be low [18].

Combined esophageal multichannel intraluminal impedance (MII) and pH testing similarly appeared to have poor utility in investigating laryngopharyngeal reflux [19]. Distal esophageal measurement of reflux has not been found to be useful in assessing laryngopharyngeal sequelae. Lee et al. examined esophageal luminal impedance and pH values in a group of patients with LPR symptoms, and reported diagnostic yields of only 37.8% in single-channel and 49% in dual-channel MII-pH measurements [3].

In the present study, reflux scintigraphy demonstrated excellent yield for directly visualising reflux phenomena in real time to the levels of the proximal esophagus and pharynx. This was seen in both groups of patients with severe symptoms likely to have a high pre-test probability of disease. Reflux scintigraphy showed a high rate of abnormal reflux in the upright pharynx and proximal esophagus in 90.4% of our LPR patients. These yields are different from other studies in the literature. Bestetti and colleagues performed reflux scintigraphy with a different technique in 201 patients with posterior laryngitis and reported early scintigraphic reflux in 66.6% of their group, 51.7% had scintigraphic reflux to the pharynx, 14.9% had scintigraphic reflux to the distal esophagus only. Laryngoscope-confirmed posterior laryngitis is likely on the severe end of the spectrum of LPR, it is therefore unsurprising that a high level of pharyngeal contamination was identified [20]. Galli et al. performed reflux scintigraphy with a different technique on 41 patients with LPR symptoms and reported a yield of 82.9% of their cohort as having morphofunctional pathologic patterns on reflux scintigraphy, though these pathologic patterns were not clearly defined [21]. Reflux scintigraphy appears to be sensitive in detecting sequalae of LPR in a cohort of patients with a high clinical probability of disease.

The GERD and LPR groups had similar rates of early and delayed pharyngeal contamination. The fact that both groups had demonstrable reflux of scintigraphic tracer to the upper aerodigestive tract is not surprising, as both groups were treatment resistant. Differing symptom profiles related to refluxed gastric contents may be due to variation in perception of symptoms, rather than the severity, frequency, or duration of acid exposure [22]. Studies have suggested that central and peripheral neural mechanisms may modulate esophageal perception [23], and there was a demonstrable lesser reflux exposure in the LPR group in the distal esophagus.

Delayed scintigraphic contamination of the lungs was seen in 46% of patients in this cohort, with a significantly greater incidence in the LPR group of patients versus the GERD group. Pulmonary aspiration was largely asymptomatic, with a single patient reporting an aspiration event. Other studies have found scintigraphic pulmonary aspiration to be of variable frequency in patients with GERD, ranging from 15 to 26% [7, 20]. The rate of pulmonary aspiration in the present GERD group was higher than historical figures. This may reflect a silent group of aspirators that have previously not been identified. Other possibilities are improved sensitivity of the modified scintigraphy technique, or a more severely diseased population examined that are silently aspirating, and have symptoms masked by severe GERD-predominant symptoms. The increased reporting may also be due to a higher sensitivity of detecting small volumes of aspirated radioactive material against less background activity, as technetium-99m DTPA, which has a high volume of distribution and higher background contribution, was not used.

Between the LPR and GERD groups, reflux scintigraphy parameters such as reflux episode frequency, AUC, and maximal amplitude were similar. Bestetti et al. reported that pharyngeal refluxers, when compared with

distal esophageal refluxers, had significantly more reflux episodes, longer duration of most severe episode, and overall duration of episodes. The present study differed to that of Bestetti et al. in some ways. Crucially, we did not define the duration of the reflux event for inclusion, unlike the other study, so Bestetti's cohort may have contained more patients with elevated acid exposure time (AET). Previous studies by the authors have demonstrated a delay in clearance by MII-pH methodology congruent with data by Bestetti et al. [20] indicative of this being a factor in pathogenesis of disease.

The LPR group being relatively older may be due to a longer diagnostic period from onset of symptoms to investigation and diagnosis. Unlike GERD, LPR is less well-defined, and with wider range of symptoms covering multiple systems [24]. Symptoms such as chronic cough may have many different aetiologies, and many LPR patients have typically seen multiple different specialties, typically otorhinolaryngologists and respiratory physicians.

The higher rate of females in this cohort of LPR patients may reflect an increased likelihood that females are more likely to seek medical attention for symptoms [25], or possibly a truly higher female incidence of disease.

Reflux scintigraphy has limitations. It does not simultaneously assess pH and does not distinguish between acidic and non-acidic reflux events. Reflux episodes are detected in a 30-min window, and not a 24-h period such as with impedance-pH assessment. It does, however, assess a 2-h period of erect events in the delayed contamination study.

Conclusion

Using a modified technique of reflux aspiration scintigraphy, we detected a high rate of pharyngeal contamination and pulmonary reflux microaspiration in tertiary referral patients with a high pre-test probability of LPR, as well as severe, treatment-resistant GERD. Proximal regurgitation events were not different between treatment-resistant GERD symptomatic patients and LPR symptomatic patients. The present modified scintigraphic technique may be valuable in the positive diagnosis of LPR, and may lead to early diagnosis. The technique may be useful in investigating pulmonary symptomatology in reflux patients, especially in LPR patients, where the frequency of pulmonary microaspiration was significantly higher.

Funding The authors have no relevant financial or non-financial interests to disclose.

Declarations

Conflict of interest The authors declare that they have no conflict of interest to disclose.

References

1. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, The Global Consensus Group (2006) The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 10(8):1900–1920. https://doi.org/10.1111/j.1572-0241.2006.00630.x
2. Houghton LA, Lee AS, Badri H, DeVault KR, Smith JA (2016) Respiratory disease and the oesophagus: reflux, reflexes and microaspiration. Nat Rev Gastroenterol Hepatol 13(8):445–460. https://doi.org/10.1038/nrgastro.2016.91
3. Lee BE et al (2010) Combined dual channel impedance/pH-metry in patients with suspected laryngopharyngeal reflux. J Neurogastroenterol Motil 16(2):157–165. https://doi.org/10.5056/jnm.2010.16.2.157
4. Harrell SP, Koopman J, Woosley S, Wo JM (2007) Exclusion of pH artifacts is essential for hypopharyngeal pH monitoring. Laryngoscope 117(3):470–474. https://doi.org/10.1097/MLG.0b013e31802d344c
5. Zerbib F et al (2013) Normal values of pharyngeal and esophageal 24-hour pH impedance in individuals on and off therapy and interobserver reproducibility. Clin Gastroenterol Hepatol 11(4):366–372. https://doi.org/10.1016/j.cgh.2012.10.041
6. Ummarino D, Vandermeulen L, Roosens B, Urbain D, Hauser B, Vandenplas Y (2013) Gastroesophageal reflux evaluation in patients affected by chronic cough: restech versus multichannel intraluminal impedance/pH metry. Laryngoscope 123(4):980–984. https://doi.org/10.1002/lary.23738
7. Khoma O, Burton L, Falk MG, Van der Wall H, Falk GL (2020) Predictors of reflux aspiration and laryngo-pharyngeal reflux. Esophagus 17(3):355–362. https://doi.org/10.1007/s10388-020-00726-9
8. Ruth M, Carlsson S, Månsson I, Bengtsson U, Sandberg N (1993) Scintigraphic detection of gastro-pulmonary aspiration in patients with respiratory disorders. Clin Physiol 13(1):19–33. https://doi.org/10.1111/j.1475-097X.1993.tb00314.x
9. Burton L, Falk GL, Parsons S, Cusi M, Van Der Wall H (2018) Benchmarking of a simple scintigraphic test for gastro-oesophageal reflux disease that assesses oesophageal disease and its pulmonary complications. Mirt 27(3):113–120. https://doi.org/10.4274/mirt.10438
10. Burton L, Falk GL, Beattie J, Novakovic D, Simpson S, Van der Wall H (2020) Findings from a novel scintigraphic gastroesophageal reflux study in asymptomatic volunteers. Am J Nucl Med Mol Imaging 10(6):342–348
11. Falk GL (2015) Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? WJG 21(12):3619. https://doi.org/10.3748/wjg.v21.i12.3619
12. Lechien JR et al (2019) Evaluation and management of laryngopharyngeal reflux disease: state of the art review. Otolaryngol Head Neck Surg 160(5):762–782. https://doi.org/10.1177/0194599819827488
13. Amarasiri DL, Pathmeswaran A, de Silva HJ, Ranasinha CD (2013) Response of the airways and autonomic nervous system to acid perfusion of the esophagus in patients with asthma: a laboratory study. BMC Pulm Med 13(1):33. https://doi.org/10.1186/1471-2466-13-33

14. Belafsky PC, Postma GN, Koufman JA (2001) The validity and reliability of the reflux finding score (RFS). Laryngoscope 111(8):1313–1317. https://doi.org/10.1097/00005537-200108000-00001
15. Milstein CF, Charbel S, Hicks DM, Abelson TI, Richter JE, Vaezi MF (2005) Prevalence of laryngeal irritation signs associated with reflux in asymptomatic volunteers: impact of endoscopic technique (rigid vs. flexible laryngoscope). Laryngoscope 115(12):2256–2261. https://doi.org/10.1097/01.mlg.0000184325.44968.b1
16. Chen M, Hou C, Chen T, Lin Z, Wang X, Zeng Y (2018) Reflux symptom index and reflux finding score in 91 asymptomatic volunteers. Acta Otolaryngol 138(7):659–663. https://doi.org/10.1080/00016489.2018.1436768
17. Hicks DM, Ours TM, Abelson TI, Vaezi MF, Richter JE (2002) The prevalence of hypopharynx findings associated with gastroesophageal reflux in normal volunteers. J Voice 16(4):564–579. https://doi.org/10.1016/S0892-1997(02)00132-7
18. Branski RC, Bhattacharyya N, Shapiro J (2002) The reliability of the assessment of endoscopic laryngeal findings associated with laryngopharyngeal reflux disease. Laryngoscope 112(6):1019–1024. https://doi.org/10.1097/00005537-200206000-00016
19. Anandasabapathy S, Jaffin BW (2006) Multichannel intraluminal impedance in the evaluation of patients with persistent globus on proton pump inhibitor therapy. Ann Otol Rhinol Laryngol 115(8):563–570
20. Bestetti A, Carola F, Carnevali-Ricci P, Sambataro G, Tarolo GL (2000) 99mTc-sulfur colloid gastroesophageal scintigraphy with late lung imaging to evaluate patients with posterior laryngitis. J Nucl Med 41(10):1597–1602
21. Galli J, Volante M, Parrilla C, Rigante M, Valenza V (2005) Oropharyngoesophageal scintigraphy in the diagnostic algorithm of laryngopharyngeal reflux disease: a useful exam? Otolaryngol Head Neck Surg 132(5):717–721. https://doi.org/10.1016/j.otohns.2005.01.043
22. Fass R (2002) Functional heartburn: the stimulus, the pain, and the brain. Gut 51(6):885–892. https://doi.org/10.1136/gut.51.6.885
23. Trimble KC, Pryde A, Heading RC (1995) Lowered oesophageal sensory thresholds in patients with symptomatic but not excess gastro-oesophageal reflux: evidence for a spectrum of visceral sensitivity in GORD. Gut 37(1):7–12. https://doi.org/10.1136/gut.37.1.7
24. Koufman JA, Amin MR, Panetti M (2000) Prevalence of reflux in 113 consecutive patients with laryngeal and voice disorders. Otolaryngol Head Neck Surg 123(4):385–388. https://doi.org/10.1067/mhn.2000.109935
25. Lin M, Gerson LB, Lascar R, Davila M, Triadafilopoulos G (2004) Features of gastroesophageal reflux disease in women. Off J Am Coll Gastroenterol 99(8):1442–1447
26. Burton L, Falk GL, Baumgart K, Beattie J, Simpson S, Van der Wall H (2020) Esophageal clearance in laryngopharyngeal reflux disease: correlation of reflux scintigraphy and 24-hour impedance/pH in a cohort of refractory symptomatic patients. Mol Imaging Radionucl Ther 29(1):7–16. https://doi.org/10.4274/mirt.galenos.2019.30085
27. Falk M, Van der Wall H, Falk GL (2015) Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms. Nucl Med Commun 36(6):625–630. https://doi.org/10.1097/MNM.0000000000000289

Esophagus (2020) 17:355–362
https://doi.org/10.1007/s10388-020-00726-9

ORIGINAL ARTICLE

Predictors of reflux aspiration and laryngo-pharyngeal reflux

Oleksandr Khoma[1,2] · Leticia Burton[3] · Michael G. Falk[4] · Hans Van der Wall[3] · Gregory L. Falk[1,4,5]

Received: 29 November 2019 / Accepted: 12 February 2020 / Published online: 21 February 2020

Abstract

Background Gastro-esophageal reflux disease (GERD) can present with typical or atypical or laryngo-pharyngeal reflux (LPR) symptoms. Pulmonary aspiration of gastric refluxate is one of the most serious variants of reflux disease as its complications are difficult to diagnose and treat. The aim of this study was to establish predictors of pulmonary aspiration and LPR symptoms.

Methods Records of 361 consecutive patient from a prospectively populated database were analyzed. Patients were categorized by symptom profile as predominantly LPR or GERD (98 GER and 263 LPR). Presenting symptom profile, pH studies, esophageal manometry and scintigraphy and the relationships were analyzed.

Results Severe esophageal dysmotility was significantly more common in the LPR group ($p=0.037$). Severe esophageal dysmotility was strongly associated with isotope aspiration in all patients ($p=0.001$). Pulmonary aspiration on scintigraphy was present in 24% of patients. Significant correlation was established between total proximal acid on 24-h pH monitoring and isotope aspiration in both groups ($p<0.01$). Rising pharyngeal curves on scintigraphy were the strongest predictors of isotope aspiration ($p<0.01$).

Conclusions Severe esophageal dysmotility correlates with LPR symptoms and reflux aspiration in LPR and GERD. Abnormal proximal acid score on 24-h pH monitoring associated with pulmonary aspiration in reflux patients. Pharyngeal contamination on scintigraphy was the strongest predictor of pulmonary aspiration.

Keywords LPR · GERD · Reflux aspiration · Esophageal motility · Scintigraphy

Background and purpose

Gastro-esophageal reflux disease (GERD) can present in a number of ways and atypical symptoms are frequently difficult to diagnose as reflux and treat. Common symptoms of GERD include heartburn and regurgitation, whilst cough, sore throat, recurrent pneumonia, globus, and hoarseness are generally regarded as "atypical" symptoms. Based on the symptom profile, GERD is sub-classified as esophageal or extraesophageal [1]. Laryngo-pharyngeal reflux (LPR) is believed to be caused by the contamination of the larynx and pharynx with gastric contents. Symptoms of chronic cough, throat clearing, and globus sensation are non-specific and can be attributed to other conditions [2, 3]. Currently, there is no reference standard for the diagnosis of LPR. Proximal pH monitoring is deficient technically as many of the proximal reflux episodes are non-acidic and cannot be reliably measured in the pharynx. Findings of impedance reflux measurements in the upper esophagus, even though not dependent on acid measurement, are often difficult to interpret [4]. Furthermore, none of the above methods have been validated in the diagnosis of cough. Untreated LPR with recurrent upper airway contamination can have serious consequences which range from paradoxical vocal cord motion to laryngeal stenosis, asthma, recurrent pneumonia, pulmonary fibrosis, and laryngeal malignancy [5, 6]. The current algorithms for work-up for GERD and LPR include history and physical examination, trans-nasal laryngoscopy and gastro-intestinal endoscopy, 24-h pH monitoring, esophageal impedance, esophageal manometry, barium swallow, and scintigraphy; none of which is definitive [7–9].

✉ Oleksandr Khoma

[1] Department of Upper Gastro-Intestinal Surgery, Concord Repatriation General Hospital, Sydney, Australia

[2] University of Notre Dame Australia, Sydney, Australia

[3] Concord Nuclear Imaging, Sydney, Australia

[4] Sydney Heartburn Clinic, Sydney, Australia

[5] University of Sydney, Sydney, Australia

Ineffective esophageal motility (IOM) has been thought to be a major factor in GERD and LPR [10, 11]. However, the exact role of the IOM has not been established [12–14]. We present the findings of esophageal manometry, dual-channel 24-h pH monitoring, and scintigraphy in two clinically distinct groups of patients classified as LPR or GERD.

We hypothesized that severe esophageal dysmotility is an important determinant of LPR and lung aspiration of refluxate. This hypothesis was tested in 361 consecutive patients with resistant to medical management reflux referred for surgical opinion.

Patients and methods

Patient population

Data were extracted from prospectively populated research database containing records of patients with GERD that was approved by the University of Notre Dame Australia Human Research Ethics Committee (019091S) on 23rd of July 2019. This study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All patient provided informed written consent to participate in research.

A senior surgical consultant assessed all patients and prospectively clinically categorized their symptoms as predominantly GERD or LPR based on the dominant symptom. Consecutive patients with symptoms typical of GERD (predominant heartburn, and chest pain) or LPR (predominant cough, throat clearing, voice change, laryngospasm, recurrent pneumonia, mucus sensation and globus) who underwent esophageal manometry, pH studies, and scintigraphy were included. All patients had been referred for surgical consideration to a tertiary referral center due to severity of symptoms and/or resistance to maximal medical therapy. The cohort is, therefore, highly selected with a high pre-test probability of severe GERD/LPR.

pH Monitoring

Antimony crystal dual-channel catheters and Digi trapper Mark III recorder (Medtronics, Synectics Medical, Minneapolis, Minnesota, USA) were used for pH monitoring and data collection as a part of assessment process. The distal esophageal probe was placed 5 cm above the manometrically identified upper border of lower esophageal sphincter, and the proximal probe placed 15 cm above the distal probe. pH data were analyzed using the Synectics PW esophagram reflux analysis module (Medtronics, Synectics Medical, Minneapolis, Minnesota, USA). Monitoring was conducted in ambulatory settings.

Manometry

Esophageal manometry was performed using a standard technique with a water-perfused dent sleeve eight-channel catheter (Dent Sleeve International, Mississauga, Ontario, Canada). Data were recorded with a multichannel recording system (PC polygraph HR Medtronics, Synectics Medical, Minneapolis, Minnesota, USA). Analysis of esophageal motility was done by the PolyGram software program (Medtronics, Synectics Medical, Minneapolis, Minnesota, USA). Esophageal motility was classified as normal (less than two ineffective swallows), mild ineffective esophageal motility (IOM) (2–3 swallows with ineffective peristalsis), moderate IOM (4–5 swallows with ineffective peristalsis), or severe IOM (six or more swallows with ineffective peristalsis) using criteria modified from Kahrilas et al. [10, 11].

Scintigraphy

Scintigraphy was conducted using computer-generated isotope counting minimizing potential inter-observer bias. This particular method of scintigraphy in diagnosis of GERD and LPR has been previously described in detail and validated by this group, and control values have been published [8, 9, 15]. Patients were fasted overnight and then placed before Hawkeye 4 gamma camera (General Electric, Milwaukee, United States) with stomach, chest, and upper airway in the field of view. Patients were administered 40–60 MBq of 99mTc DTPA diluted in 150 ml of water, followed by a 50-ml water to promote clearance of isotope from pharynx and esophagus. Images were obtained for 2 min at 15 s per frame into a 64×64 matrix, followed by a 30-min dynamic image while supine for 30 s per frames. Aspiration was proven on delayed images at 2 h by the presence of isotope in the lungs (Fig. 1). Isotope time-activity curves (Fig. 2) were recorded for the pharynx and upper esophagus supine and erect, and classified as falling, flat, or rising curves (Fig. 3). It was considered that a falling curve reflected clearance of refluxate and rising curve accumulation of refluxate.

Statistical analysis

Data analysis was undertaken using nonparametric statistical methods as much of the analysis was of ordinal data with multiple studies for each patient. Analysis of variance (ANOVA), Mann–Whitney *U* test, Student's *t* test, Fisher's exact test, and Pearson/Spearman correlation coefficient (two-tailed) with significance levels of 0.05 were utilized. Receiver-operating characteristics (ROC) were assessed to evaluate the best predictors for pulmonary aspiration. Cluster analysis of the principal

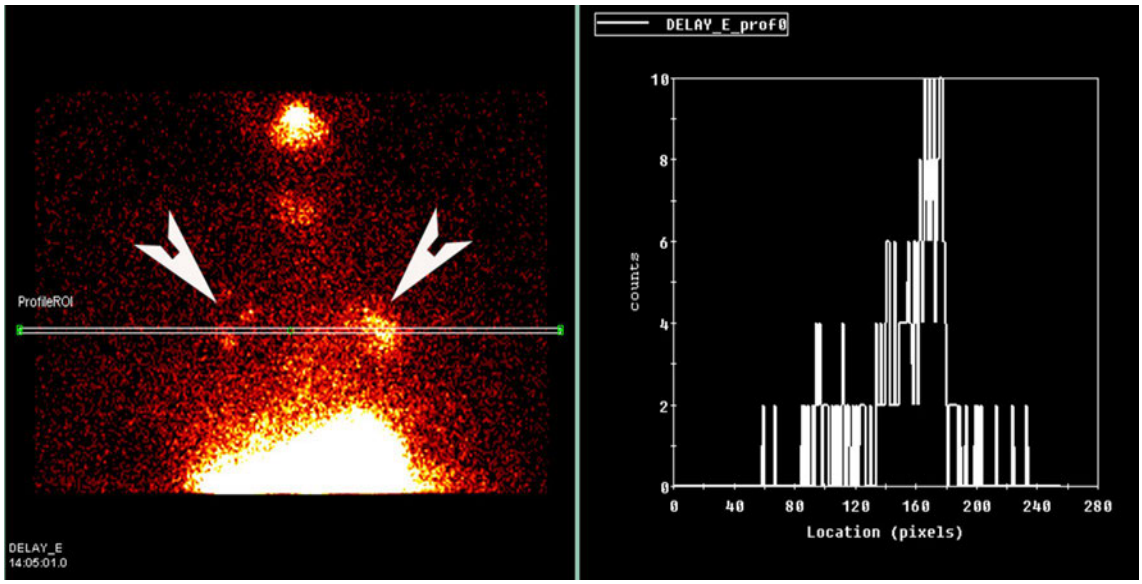


Fig. 1 Left of the screen is a delayed scintigraphy study showing aspiration of tracer into both lungs (white arrowheads) and the double white-line marking for computer-generated isotope count. Right of the screen is a computerized report as profile showing the count through the regions white lines. A high isotope count is apparent for the left lung activity (location 160–190 pixels)

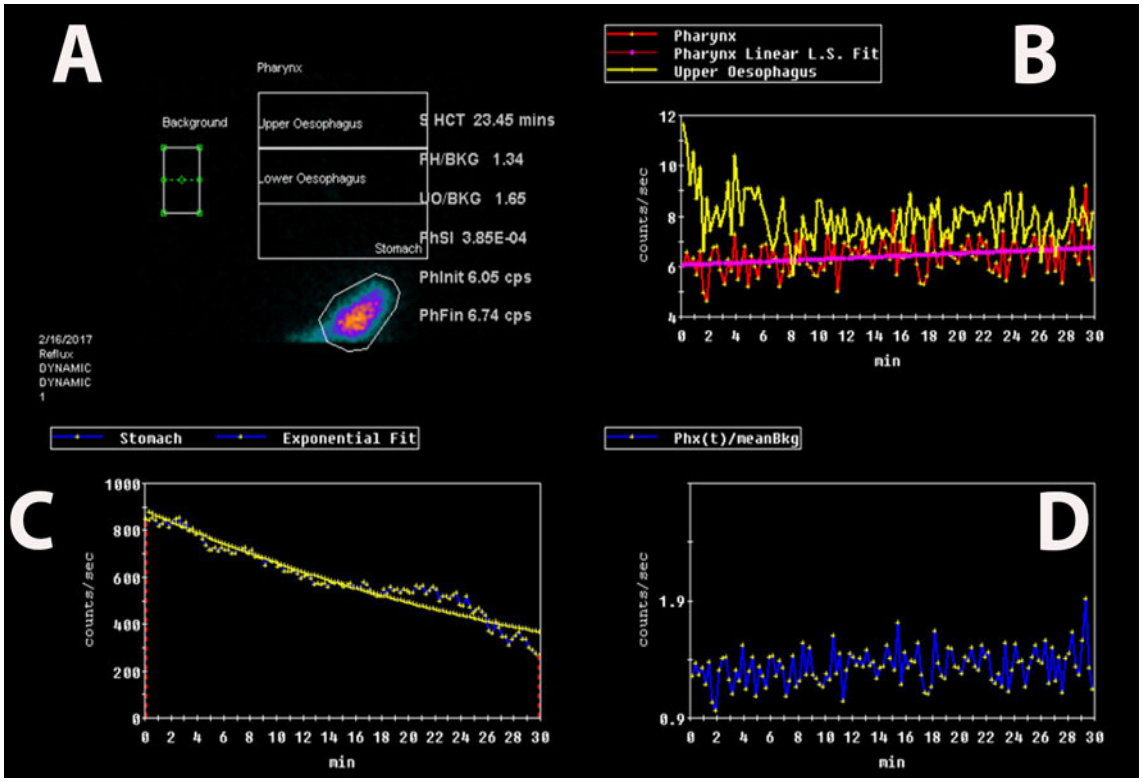


Fig. 2 Typical graphical analysis of the scintigraphic study showing the markings of the regions of interest for the pharynx, esophagus, stomach, and background in the top left panel (**a**). **b** Analysis of the time-activity curves for the pharynx (pink/red) and upper esophagus (yellow). A rising curve is apparent for the pharynx (purple line ascending). **c** Fitted curve for estimation of liquid gastric emptying which has a time to half clearance of 22.5 min (shown in panel A). **d** Graphical representation of the ratio of pharyngeal-to-background time-activity curves (mildly raising time-activity curves indicate low-volume reflux contamination)

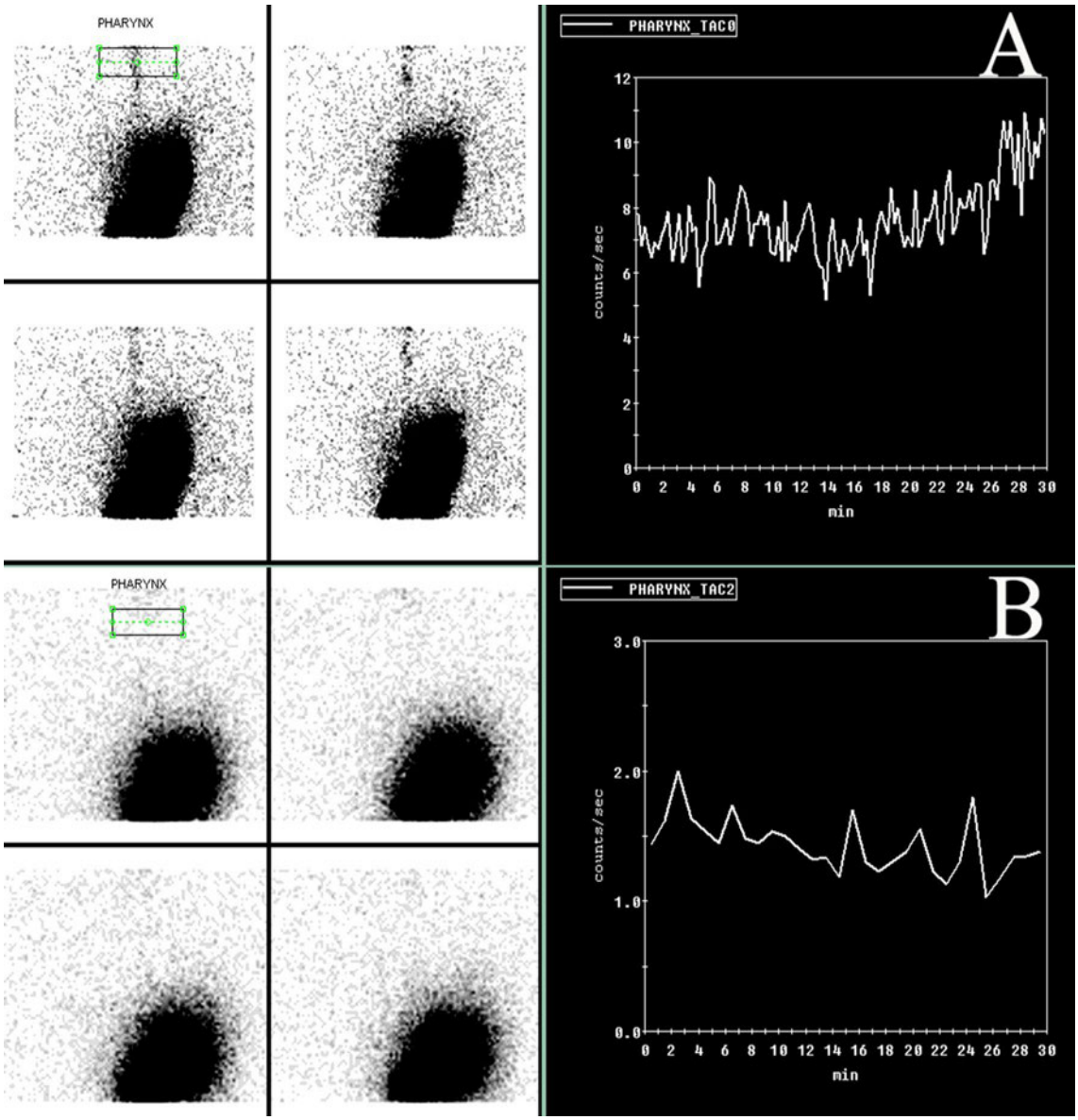


Fig. 3 Typical graphic analysis showing computer-generated count for isotope contamination in the pharynx. To the left of the screen, there are scintigraphic images marked for counting and to the right of the screen graphs showing results for the areas marked. Y-axis reflects isotope count and X-axis reflects time of study. Panel A showing clearly rising isotope count (contamination due to reflux), whilst panel B showing flat count (no evidence of reflux reaching pharynx)

variables was undertaken to evaluate linkages between ten key variables and for the groups (LPR vs. GERD). Cluster analysis is a multivariate procedure for detecting natural groupings in data [16]. Euclidean distance (root-mean-squared) was utilized and displayed as a vertical icicle plot. Univariate and multivariate analyses were used to evaluate possible etiologies of dominant symptom profiles (LPR vs. GERD). The Statistica V8 software (Statsoft, Oklahoma, United States) package was used for data analysis.

Results

Population and clinical data

Inclusion criteria were met by 361 patients (223 female and 138 male). The mean age was 60.8 years (SD 14.6; range 16–90 years). There were 98 patients in the GERD subgroup (47 female and 51 male) with average age of 56 years (SD 13.61, range 23–84). The LPR subgroup

Table 1 Demographic characteristics and summary of the main findings of this study according to the symptom profile group

	GERD	LPR	All patients
Number of patients			
Male	51	176	227
Female	47	87	134
Total	98	263	361
Age			
Average	56	63	60.8
SD	13.61	14.95	14.6
Range	23–84	16–90	16–90
LOS pressure mean (mmHg)[a]	7.4	6.9	7.0 (95% CI 6.1–7.8)
Severe IOM[b]			
n	29	105	134
%	28%	40%	37%
Pulmonary aspiration[c]			
n	19	75	94
%	19%	29%	26%
24-h pH proximal acid exposure[d]			
n abnormal	32	71	103
Mean time %/24 h (SD)	0.9% (SD 4.3)	1.9% (SD 6.4)	1.8% (SD 6.2)

[a]Reduced LOS was associated with pulmonary aspiration ($p=0.001$) and proximal esophageal acid exposure ($p=0.019$)

[b]Significant difference between the groups ($p=0.037$)

[c]Result did not reach statistical significance ($p=0.08$)

[d]Proximal esophageal acid exposure on 24-h pH monitor was associated with pulmonary aspiration ($p=0.003$)

included 263 patients (176 female and 87 male) and mean age of 63 years (SD 14.95, range 16–90).

Patient demographic data and key results are summarized in Table 1.

Manometry

The outstanding feature of manometric findings was that 40% of the LPR group patients had severe IOM compared with 28% in the GERD group. This was a significant difference ($p=0.037$). Normal esophageal motility was found in 48% with LPR symptoms and in 60% with GERD symptoms, and was not statistically significant.

The mean lower esophageal sphincter pressure was reduced at 7.0 mm Hg (Median 3.4, SD 8.1 (95% CI 6.1–7.8) mm Hg). No significant difference was found between the LPR and GERD groups for mean LOS pressure.

Manometry: correlations between IOM, aspiration, and symptom profile

Severe IOM was strongly associated with isotope aspiration in both groups ($p=0.001$).

There was a strong correlation (Spearman) between IOM and isotope curves in the pharynx and upper esophagus both when supine and upright ($p<0.01$).

Significantly more rising isotope activity curves (grade 3) were demonstrated in patients with LPR than with GERD symptoms ($p=0.0017$). There was, however, no statistically significant difference in isotope aspiration between the groups ($p=0.08$).

Reduced lower esophageal sphincter pressure was associated with an increased proximal acid exposure ($p=0.019$) and risk of isotope aspiration ($p=0.001$).

pH Studies

pH Studies were abnormal in 70% of patients. Total proximal acid exposure was a mean of 4.2%/24 h (SD 6.2). Total distal acid exposure was a mean of 9.3%/24 h (SD 12.7).

pH Studies: correlation of aspiration and pH study

There was a correlation between total proximal acid on 24-h pH monitoring and pulmonary isotope aspiration ($p=0.003$) in both groups. There was no correlation between total distal acid on 24-h monitoring and aspiration ($p=0.87$).

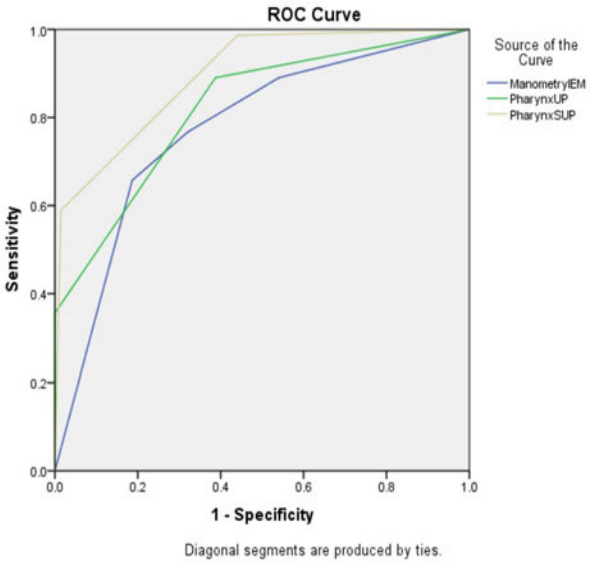
Scintigraphic studies

Aspiration of refluxate into the lungs was found in 94 patients (26%). When examined by symptom profile, there were 19 patients in the GERD group (19%) and 75 (29%) in the LPR group with pulmonary aspiration.

Scintigraphic parameters and pulmonary aspiration

Rising activity curves in the pharynx were strong predictors of isotope aspiration ($p < 0.01$), both when upright and supine. While a higher proportion of patients with aspiration were from the group with LPR symptoms (29% vs. 19%), this apparent difference was not significant with the two-tailed Fisher's exact test ($p = 0.08$).

For all patients, the negative predictive value of a declining time-activity curve for aspiration for the pharynx in the upright and supine positions was 98%. A rising time-activity curve for the pharynx in the upright and supine position had a positive predictive value of 88% for aspiration. A similar pattern for the esophageal curves gave a negative predictive value of 97% and a positive predictive value of 85%.



Area Under the Curve

Test Result Variable(s)	Area
ManometryIEM	.773
PharynxUP	.820
PharynxSUP	.896

Fig. 4 Receiver-operating characteristic (ROC) analysis. Pharyngeal supine activity is the best predictor of lung aspiration of refluxate, followed by pharyngeal upright activity and manometry

Receiver-operating characteristic (ROC) analysis of pulmonary aspiration

The three best variables for predicting aspiration were the presence of severe IOM and the rising time-activity curves for pharyngeal tracer activity in the upright and supine positions. This is clearly shown in Fig. 4. The largest area under the curve was for pharyngeal tracer activity when supine (0.896) followed by the pharyngeal curve when upright (0.820) and severe IOM (0.773).

Cluster analysis

The purpose of luster analysis is to simply demonstrate central role of IEM in patients with pulmonary aspiration.

Strong linkages were found between pulmonary aspiration demonstrated by scintigraphy, all scintigraphic time-activity curves for the upper esophagus and pharynx, IOM, and clinical symptom profile (Fig. 5).

Discussion

The diagnosis of laryngo-pharyngeal reflux (LPR) is a clinical challenge. Clinical scoring systems to establish the probability of LPR in patients with upper aero-digestive symptoms have been proposed in the past [17]. Between 18.5% and 30% of general population will test as having high probability of LPR using the current Reflux Symptom Index, which is also reported to be an overestimation of the true incidence of LPR [18, 19]. Hull Airway Reflux Questionnaire is a useful and validated tool in diagnosing LPR

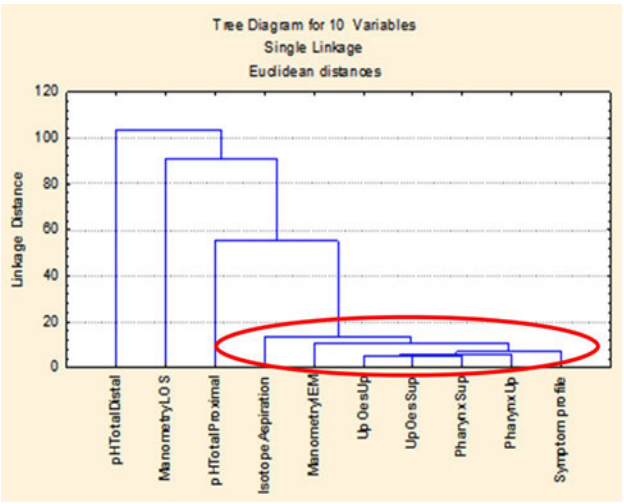


Fig. 5 Cluster analysis. The analysis shows tight linkages between manometry, upright and supine pharyngeal and upper esophageal scintigraphic activity, and the patient symptom profile

symptoms due to reflux. However, it is a screening tool and does not positively diagnose airway reflux [20].

Scintigraphic study using the described technique may demonstrate, where no other test can, a significant proportion (~20%) of patients with severe GERD who also have clinically silent pulmonary aspiration.

A less foreseen but suspected result of this study was the association between esophageal dysmotility and lung aspiration of refluxate, as shown in the ROC analysis. Manometric measures of the lower esophageal sphincter pressures did not discriminate for this complication, as low pressures had a high prevalence in this treatment-resistant group of patients, reflecting disease severity. The prevalence of severe IOM was not significantly different between the LPR and GERD groups. This may be due to a selection bias as GERD patients in this cohort represent the more severe end of the spectrum of disease resistant to maximal medical therapy.

The importance of identifying patients with pulmonary aspiration is of patent clinical importance due to the potential for irreversible changes in the laryngopharynx and lungs. Preliminary data from an ongoing study of 120 patients with scintigraphic evidence of pulmonary aspiration show that while medical therapy may improve the symptoms of LPR or GERD, it does not reverse pulmonary aspiration [15].

Pulmonary aspiration can be treated with laparoscopic fundoplication with improvement demonstrated by scintigraphy as well as clinical resolution of symptoms [8, 21]. Previous work by this group found that over 90% of patients with clinical and scintigraphic evidence of LPR pre-operatively reported significant resolution of symptoms and scan improvement after surgery [8, 21].

Early research on esophageal dysmotility has suggested reduced esophageal clearance in individuals with IOM [22, 23]. In this study, patients showed a high degree of impaired esophageal motility, which was associated with pulmonary aspiration. The presence of refluxate in the upper esophagus can stimulate cough via "reflex" afferent pathways and the presence of gastric contents in the pharynx can cause direct irritation to the upper airways, also resulting in cough [24]. The impairment of esophageal clearance secondary to diminished esophageal motility may offer a plausible explanation for the development of symptoms through combined "reflux" and "reflex" pathways, allowing continued esophageal exposure or proximal exposure to gastric contents [25].

In our cohort, the average age in the LPR group was 7 years greater than the GERD group. Reasons for this variance are unclear. Many alternative causes of atypical reflux symptoms may require serial elimination extending the period to diagnosis. The lack of a simple positive predictive test for diagnosis of LPR may also contribute. Upper aero-digestive contamination was frequent in the GERD group. Delayed development of respiratory symptoms from the pulmonary disease could be due to changes in the mucociliary escalator defense mechanisms as a result of chronic exposure to gastric contents, further delaying time to diagnosis [5, 26]. Perhaps, trivializing the symptoms by the patient and the medical profession may contribute to delayed presentation and referral.

Limitations of this study were the collection of data over 8 years during which time the technique of scintigraphy was refined. There is substantial selection bias as all patients in this study were referred for consideration of surgery due to severity of symptoms and often multiple failed therapeutic strategies.

Conclusion

Severe esophageal dysmotility, raised proximal acid on 24-h pH monitoring, and pharyngeal contamination on scintigraphy are associated with pulmonary aspiration and LPR symptoms. Upper aero-digestive tract contamination with reflux is common in patients with LPR and severe treatment-resistant GERD. The results of this study indicate that reflux scintigraphy by this particular technique is invaluable in assessing patients with severe GERD, LRP, and unexplained pulmonary symptoms.

Funding No funding was received towards this research. Research database is approved by the University of Notre Dame Australia Human Research Ethics Committee (019091S) on 23rd of July 2019.

Compliance with ethical standards

Ethical statement This research conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent All patient provided informed written consent to participate in research.

References

1. Vakil N, Van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101:1900–20.
2. Barry DW, Vaezi MF. Laryngopharyngeal reflux: more questions than answers. Clevel Clin J Med. 2010;77:327–34.
3. Martinucci I, de Bortoli N, Savarino E, et al. Optimal treatment of laryngopharyngeal reflux disease. Ther Adv Chronic Dis. 2013;4:287–301.
4. Ravi K, Katzka DA. Esophageal impedance monitoring: clinical pearls and pitfalls. Am J Gastroenterol. 2016;111:1245–56.
5. Lee JS, Collard HR, Raghu G, et al. Does chronic microaspiration cause idiopathic pulmonary fibrosis? Am J Med. 2010;123:304–11.

6. Postma GN, Halum SL. Laryngeal and pharyngeal complications of gastroesophageal reflux disease. GI Motil. 2006. https://doi.org/10.1038/gimo46.
7. Abou-Ismail A, Vaezi MF. Evaluation of patients with suspected laryngopharyngeal reflux: a practical approach. Curr Gastroenterol Rep. 2011;13:213–8.
8. Falk GL, Beattie J, Ing A, et al. Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? World J Gastroenterol. 2015;21:3619–27.
9. Falk M, Van der Wall H, Falk GL. Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms. Nucl Med Commun. 2015;36:625–30.
10. Kahrilas PJ, Dodds WJ, Hogan WJ, et al. Esophageal peristaltic dysfunction in peptic esophagitis. Gastroenterology. 1986;91:897–904.
11. Kahrilas PJ, Dent J, Dodds WJ, et al. A method for continuous monitoring of upper esophageal sphincter pressure. Dig Dis Sci. 1987;32:121–8.
12. Simrén M, Silny J, Holloway R, et al. Relevance of ineffective oesophageal motility during oesophageal acid clearance. Gut. 2003;52:784–90.
13. Fornari F, Blondeau K, Durand L, et al. Relevance of mild ineffective oesophageal motility (IOM) and potential pharmacological reversibility of severe IOM in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2007;26:1345–54.
14. Abdel Jalil AA, Castell DO. Ineffective esophageal motility (IEM): the old-new frontier in esophagology. Curr Gastroenterol Rep. 2016;18:1.
15. Burton L, Falk GL, Parsons S, et al. Benchmarking of a simple scintigraphic test for gastro-oesophageal reflux disease that assesses oesophageal disease and its pulmonary complications. Mol Imaging Radionucl Ther. 2018;27:113–20.
16. Scott AJ, Knott M. A cluster analysis method for grouping means in the analysis of variance. Biometrics. 1974;30:507–12.
17. Koufman JA, Aviv JE, Casiano RR, et al. Laryngopharyngeal reflux: position statement of the committee on speech, voice, and swallowing disorders of the American Academy of Otolaryngology-Head and Neck Surgery. Otolaryngol Head Neck Surg. 2002;127:32–5.
18. Kamani T, Penney S, Mitra I, et al. The prevalence of laryngopharyngeal reflux in the English population. Eur Arch Otorhinolaryngol. 2012;269:2219–25.
19. Spantideas N, Drosou E, Bougea A, et al. Laryngopharyngeal reflux disease in the Greek general population, prevalence and risk factors. BMC Ear Nose Throat Disord. 2015;15:7.
20. Morice A, Spriggs J, Bell A. Utility of the Hull airways reflux questionnaire in the assessment of patients in the acute admissions unit. Eur Respir J. 2011;38:3513.
21. Khoma O, Falk SE, Burton L, et al. Gastro-oesophageal reflux and aspiration: does laparoscopic fundoplication significantly decrease pulmonary aspiration. Lung. 2018;196:491–6.
22. Chen CL, Szczesniak MM, Cook IJ. Identification of impaired oesophageal bolus transit and clearance by secondary peristalsis in patients with non-obstructive dysphagia. Neurogastroenterol Motil. 2008;20:980–8.
23. Kahrilas PJ, Dodds WJ, Hogan WJ. Effect of peristaltic dysfunction on esophageal volume clearance. Gastroenterology. 1988;94:73–80.
24. Irwin RS. Chronic cough due to gastroesophageal reflux disease: ACCP evidence-based clinical practice guidelines. Chest. 2006;129:80s–94s.
25. Phua SY, McGarvey LP, Ngu MC, et al. Patients with gastro-oesophageal reflux disease and cough have impaired laryngopharyngeal mechanosensitivity. Thorax. 2005;60:488–91.
26. Pearson JP, Parikh S, Orlando RC, et al. Reflux and its consequences the laryngeal, pulmonary and oesophageal manifestations. Conference held in conjunction with the 9th International Symposium on Human Pepsin (ISHP) Kingston-upon-Hull, UK, 21–23 April 2010. Aliment Pharmacol Ther. 2013;33(Suppl 1):1–71.

original article

Eur Surg
https://doi.org/10.1007/s10353-020-00632-5

european surgery
ACA Acta Chirurgica Austriaca

How effective is the control of laryngopharyngeal reflux symptoms by fundoplication? Symptom score analysis

Gregory L. Falk · Suzanna C. Gooley · Neal G. Church · David S. Rangiah

Received: 13 February 2020 / Accepted: 17 February 2020

Summary
Background The diagnosis and management of laryngopharyngeal reflux (LPR) symptoms are made difficult by the lack of good standard tests for diagnosis and for assessment of responsiveness to medical therapy. Proximal esophageal 24-h pH reading may help identify a group of patients likely to benefit from surgery.
Methods A consecutive cohort of patients from a prospective populated database were identified. Further review was undertaken by an independent investigator for symptomatic evaluation following fundoplication 24 months after surgery.
Results There were 90 patients (70% female) treated by fundoplication. The 24-h pH study was successful in 68 patients; abnormal test results were found in 62 patients. Two clinical groups of patients were identified (GORD predominant/LPR predominant) with better control of LPR symptoms in the mixed GOR/LPR cohort but improved overall ($p < 0.01$). Symptom control was incomplete.
Conclusion In selected patients with elevated proximal pH readings, symptom improvement of LPR can be achieved by fundoplication.

Keywords Laryngopharyngeal reflux disease (LPR) · Symptom control · Laparoscopic fundoplication · Proximal 24-h pH · Extra-esophageal reflux

Key novel aspects

- Results of fundoplication performance for laryngopharyngeal reflux disease (LPR) symptoms
- Selection of LPR patients by proximal 24-h pH readings
- Demonstration that quality of life improvement of LPR in patients with typical symptoms is substantially better than in patients with atypical symptoms alone

Introduction

Laryngopharyngeal reflux disease (LPR) has long been difficult to diagnose and treat [1–4]. This syndrome is considered to be caused by exposure of the upper aerodigestive tract to reflux of gastric content [5]. Once patients have been identified as resistant to medical therapy and objective tests indicate that the likely diagnosis is laryngopharyngeal reflux disease in one of its forms, then laparoscopic antireflux surgery (LARS) may be considered. Results with this approach have been mixed [6, 7]. An appreciation of the likelihood of controlling symptoms is important when offering surgery to patients, and the selection of patients with a higher probability of improvement is also important. Use of the reflux score well be helpful in assessing the outcome of this patient group (Belafsky score; [8]).

G. L. Falk, MBBS, FACS, FRACS (✉) · N. G. Church, BSc, MD, FRCSC · D. S. Rangiah, MBBS. MS. FRACS
Concord Hospital, Hospital Road, 2129 Concord, NSW, Australia
sydney.heartburn@gmail.com

N. G. Church, BSc, MD, FRCSC
neal.church@albertahealthservices.ca

D. S. Rangiah, MBBS. MS. FRACS
david.rangiah@anu.edu.au

G. L. Falk, MBBS, FACS, FRACS · S. C. Gooley, BAdvSci(Hons)
Sydney Heartburn Clinic, Suite 29/12–18 Tryon Road, 2070 Lindfield, NSW, Australia
suzanna.gooley@gmail.com

Published online: 09 March 2020

Table 1 Reflux symptoms index as defined by Belafsky 2002 [8]

Within the last month, how did the following problems affect you?	0 = no problem, 5 = all the time					
Hoarseness or a problem with your voice	0	1	2	3	4	5
Clearing your throat	0	1	2	3	4	5
Excess throat mucous or postnasal drip	0	1	2	3	4	5
Difficulty swallowing food, liquid, or pills	0	1	2	3	4	5
Coughing after you ate or after lying down	0	1	2	3	4	5
Breathing difficulties or choking episodes	0	1	2	3	4	5
Troublesome or annoying cough	0	1	2	3	4	5
Sensations of something sticking in your throat or a lump in the throat	0	1	2	3	4	5
Heartburn, chest pain, indigestion, or stomach acid coming up	0	1	2	3	4	5

Methods

Data of consecutive patients referred primarily for management of laryngopharyngeal reflux symptomatology were systematically recorded from 2001. Patients were classified as having pure laryngopharyngeal reflux (those with no heartburn), or mixed gastroesophageal reflux with laryngopharyngeal reflux (having both typical and atypical symptomatology). Patients with heartburn and regurgitation without LPR symptoms were not part of this report. Patients were required to: have a normal chest x-ray, elimination of drugs causing cough, have consultation with a respiratory medicine specialist to exclude an alternative diagnosis, have gastroenterology and endoscopy assessments, be a non-smoker, have a partial or transient response to medical therapy, and continue being symptomatic on proton pump inhibition (PPI) therapy after 6 weeks of continuous therapy with a double dose of PPI. A combination of two or more symptoms of a suggestive clinical picture, objective physical findings on laryngoscopy, and a positive 24-h proximal pH study were considered as relative indications for surgery.

Symptoms were evaluated by a senior consultant surgeon preoperatively. Symptoms were re-evaluated at 3 months after LARS for laryngopharyngeal reflux symptoms and side effects. Patients were scored on a pro forma according to the reflux symptom index of Belafsky 2002 ([8]; Table 1). A further evaluation of symptomatic outcome was performed approximately 2 years after surgery, by telephone interview performed by an independent surgical upper gastrointestinal specialist during post-fellowship experience (NC). Symptoms were evaluated and recorded and an overall satisfaction score ("Would surgery be requested knowing the outcome currently?") was obtained.

Laparoscopic antireflux surgery was not tailored for manometric measurement of esophageal body motility and patients underwent a 360° standard two-stitch Rosetti-style fundoplication over a 60-Fr Bougie with posterior closure of the hiatus using a non-absorbable suture. In short women, a 56-Fr bougie was used. Short gastric vessels were divided as required technically.

A 24-h pH dual-channel study was performed with the usual technique using Synectics Digitrapper and dual-channel antimony electrodes separated by 15 cm and the distal probe 5 cm above the upper border of the manometrically identified lower esophageal sphincter (Mark III Digitrapper, Synectics Medical AB, Sweden). Manometry was performed using an eight-channel multilumen dent sleeve water-perfused catheter (Dentsleeve, Ontario, Canada).

Results

The database contained 90 patients (70% female), with symptomatic pure LPR in 26% ($n=23$) and mixed LPR/GOR in 74% ($n=67$). A successful dual-channel 24-h pH study was performed on 68 patients. A total of 62 patients had abnormal acid exposure in the proximal esophagus and all patients had abnormal distal acid exposure. The mean number of reflux acid events was 56 in the proximal esophagus and acid exposure time was a mean of 3.2% (normal = less than 1.2).

The interview was completed in 84% ($n=76$) of patients. The median length of follow-up was 22 months. The reflux symptom index improved in all categories ($p<0.03$; Fig. 1). The LPR-specific quality of life index improved statistically significantly in each group ($p<0.01$; Fig. 2). It is noteworthy that complete resolution of symptoms was rare (12%). Improvements in the groups and overall are outlined in Fig. 3, showing the reflux symptom index (RSI) response. Response was considerably better in the mixed group. Quality of life improved in 77% of patients in the mixed group but only 53% of the pure LPR group (Fig. 4). New dysphagia occurred in 5% of patients and bloating and flatulence in 7%. Patient satisfaction improved substantially (Fig. 5).

Discussion

The symptomatic outcome of a relatively large series of patients with LPR-based symptoms following antireflux surgery is not readily available in the litera-

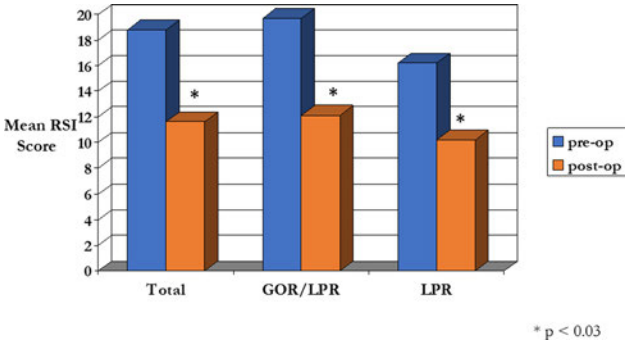


Fig. 1 Graph showing the mean score of the reflux symptom index (*RSI*) for both groups preoperatively and postoperatively, with a significant difference (*$p < 0.03$) found in all groups. Higher scores signify worse symptoms. *GOR* gastroesophageal reflux, *LPR* laryngopharyngeal reflux

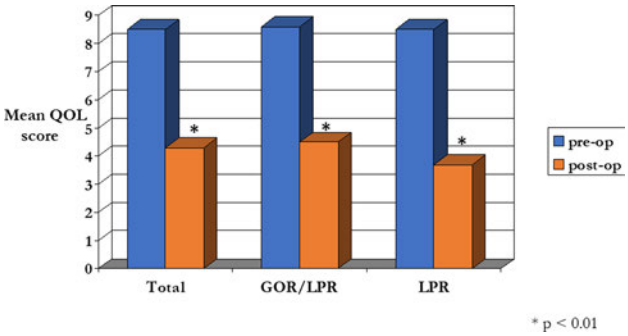


Fig. 2 Graph showing the mean scores of laryngopharyngeal reflux(*LPR*)-specific quality of life (*QoL*) scores in each patient group, with a significant difference found between each group (*$p < 0.01$), with higher scores indicating worse symptomatic reports. *GOR* gastroesophageal reflux

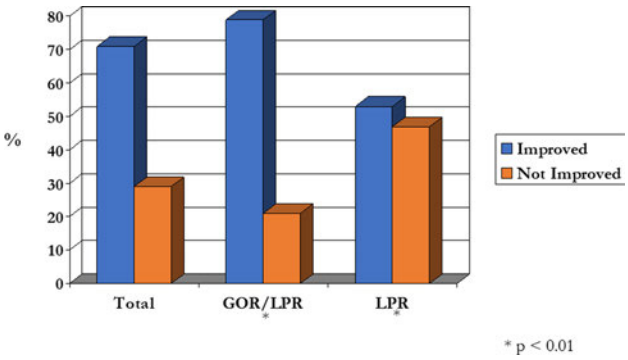


Fig. 3 Reported improvement in reflux symptom score for each group (*$p < 0.01$). *GOR* gastroesophageal reflux, *LPR* laryngopharyngeal reflux

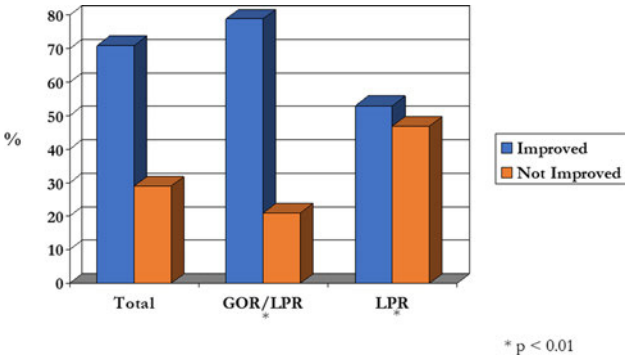


Fig. 4 Improvement in quality of life scores for each patient group (*$p < 0.01$). *GOR* gastroesophageal reflux, *LPR* laryngopharyngeal reflux

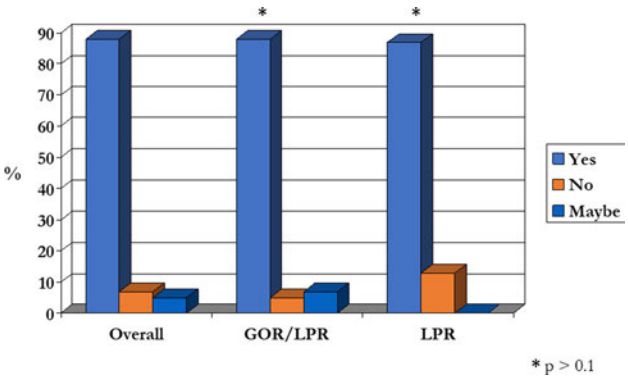


Fig. 5 Patient satisfaction with surgery, as measured by the response to "Would you have surgery again?" (*$p < 0.01$). *GOR* gastroesophageal reflux, *LPR* laryngopharyngeal reflux

ture. It was therefore thought worthwhile to add this experience of incomplete response in LPR symptomatology previously only available in abstract form [9]. Clinical subgroups appear to have different outcomes, which may relate to variations in patterns of reflux between the two groups, allowing for the potential for clinical selection that would be advantageous to outcome [10, 11]. A strong association has been found between esophageal physiological abnormalities of peristalsis, lower esophageal sphincter pressure, and proximal 24-hpH abnormality but less so for distal 24-h pH abnormality [12]. Other groups have also demonstrated the association between proximal reflux events and esophageal body dysfunction [13]. A recent study [14] demonstrated the importance of esophageal body function, which was found to be highly significant in the effectiveness of fundoplication preventing reflux pulmonary aspiration. Since the level of dysmotility in the esophagus appears to be substantially higher in the LPR group than in the GORD group, this may be an explanation for the incompleteness of proximate symptom control [6, 15]. A similar partial response of 68% to cough (part of the LPR symptom profile) was reported, as seen in our patient group. We did not find that the symptom association probability of 24-h pH analysis predicted a good response. It seems that using pH technology is unable to predict good control of pharyngeal and pharyngeal symptoms. Perhaps this is explained by the more recent recognition of non acid reflux episodes in the pharynx contribute to the disease process [16].

Of note, patients with a mixed pattern of symptoms in their medical history, both LPR and typical reflux symptoms, had substantially better symptomatic re-

sults. This may enable a refined selection of patients for improved surgical results.

Performance of fundoplication with esophageal body dysmotility probably narrows the margin for postoperative dysphagia, which was seen in this study. An alternative technique can be utilized to lessen the incidence of bolus obstruction ("post-sling"; [17]). Mixed reports of tailoring of fundoplication, according to esophageal dysmotility, are present in the literature [18, 19]. This patient group had a high proportion of elevated proximal acid exposure and represents a severe end of the spectrum of LPR disease.

Conclusion

A significant improvement in overall symptom scores was seen in patients for whom medical therapy failed—and after other causes of laryngopharyngeal reflux (LPR) symptoms were excluded—and who had abnormal proximal 24-h pH studies. Total symptom resolution, however, was rare. Patients with LPR symptoms alone appeared less likely to have symptomatic improvement following surgery; however, they reported equal levels of satisfaction to an unexplained degree. Preoperative dual-channel 24-h pH testing does not clearly identify a group of patients for whom surgery may be predictably efficacious.

Compliance with ethical guidelines

Conflict of interest G.L. Falk, S.C. Gooley, N.G. Church and D.S. Rangiah declare that they have no competing interests. No funding was received for this project and none of the authors had received research support for this project.

Ethical standards All procedures performed in studies involving human participants or on human tissue were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. *Institution*: Repatriation Gen Hospital Concord, Hospital Road Concord Sydney New South Wales Australia; *Ethics approval*: institutional ethics approval CH62/6/2011-092.

References

1. Smith JA, Houghton LA. The oesophagus and cough: laryngo-pharyngeal reflux, microaspiration and vagal reflexes. Cough. 2013;9(1):12.
2. Falk GL, Vivian S. Laryngopharyngeal reflux: diagnosis, treatment and latest research. Acta Chir Austriaca. 2016;48(2):74–91.
3. Koufman JA. Laryngopharyngeal reflux is different from classic gastroesophageal reflux disease. Ear Nose Throat J. 2002;81(9):7–9.
4. Irwin RS. Chronic cough due to gastroesophageal reflux disease: aCCP evidence-based clinical practice guidelines. Chest. 2006;129(1):80S–94S.
5. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R, Globale K. The Montreal definition and classification of gastroesophageal reflux disease: a global, evidence-based consensus paper. Z Gastroenterol. 2007;45(11):1125–40.
6. Díaz Vico T, Elli EF. Clinical outcomes of gastroesophageal reflux disease-related chronic cough following antireflux fundoplication. Esophagus. 2019;17:92–98. https://doi.org/10.1007/s10388-019-00701-z
7. Vaezi MF, Brill JV, Mills MR, Bernstein BB, Ness RM, Richards WO, et al. An episode payment framework for gastroesophageal reflux disease. Gastroenterology. 2016;150(4):1019–25.
8. Belafsky PC, Postma GN, Koufman JA. Validity and Reliability of the Reflux Symptom Index (RSI). J Voice. 2002;16(2):274–7.
9. Church N, Falk G, Rangiah D. P39 Laryngo-pharyngeal Reflux: quality of life after laparoscopic fundoplication. J Clin Gastroenterol. 2006;40:S206.
10. Burton L, Falk GL, Parsons S, Cusi M, Van Der Wall H. Benchmarking of a simple scintigraphic test for gastro-oesophageal reflux disease that assesses oesophageal disease and its pulmonary complications. Mol Imaging Radionucl Ther. 2018;27(3):113–20.
11. Falk M, Van der Wall H, Falk GL. Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms. Nucl Med Commun. 2015;36(6):625–30.
12. Falk GL, Beattie J, Ing A, Falk SE, Magee M, Burton L, et al. Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? World J Gastroenterol. 2015;21(12):3619–27.
13. Burke JM, Jackson W, Morice AH. The role of high resolution oesophageal manometry in occult respiratory symptoms. Respir Med. 2018;138:47–9.
14. Khoma O, Falk SE, Burton L, Van der Wall H, Falk GL. Gastro-oesophageal reflux and aspiration: does laparoscopic fundoplication significantly decrease pulmonary aspiration? Lung. 2018;196(4):491–6.
15. Kastelik JA, Redington AE, Aziz I, Buckton GK, Smith CM, Dakkak M, et al. Abnormal oesophageal motility in patients with chronic cough. Thorax. 2003;58(8):699–702.
16. Mainie I, Tutuian R, Shay S, Vela M, Zhang X, Sifrim D, et al. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. Gut. 2006;55(10):1398.
17. Falk GL, D'Netto TJ. Hiatal repair to reduce dysphagia in patients with impaired oesophageal motility having 360° fundoplication: the posterior 'sling' repair. Eur Surg. 2015;47(6):346–9.
18. Pizza F, Rosetti G, Del Genio G, Maffettone V, Brusciano L, Del Genio A. Influence of esophagealmotility on the outcome of laparoscopic total fundoplication. Dis Esophagus. 2008;21(1):78–85.
19. Montenovo M, Tatum RP, Figueredo E, Martin AV, Vu H, Quiroga E, et al. Does combined multichannel intraluminal esophageal impedance and manometry predict postoperative dysphagia after laparoscopic Nissen fundoplication? Dis Esophagus. 2009;22(8):656–63.

Original Article

chronic illness

Chronic Illness
0(0) 1–13

DOI: 10.1177/1742395320966373
journals.sagepub.com/home/chi
SAGE

The burden of gastroesophageal reflux disease on the cost of managing chronic diseases in Australia. The need for a new diagnostic and management paradigm

Leticia Burton[1], John Beattie[2], Gregory L Falk[3], Hans Van der Wall[1] and William Coman[4]

Abstract

Introduction: Chronic disease poses a major problem for the Australian healthcare system as the leading cost-burden and cause of death. Gastroesophageal reflux disease (GORD) typifies the problems with a growing prevalence and cost. We hypothesise that a scintigraphic test could optimise the diagnosis, especially in problematic extraoesophageal disease.

Materials and Methods: Data was collected from 2 groups of patients. Patients undergoing fundoplication for severe GORD (n = 30) and those with atypical symptoms (n = 30) were studied by scintigraphy and 24-hour oesophageal pH, impedance and manometry.

Results: Mean age of cohort was 55.8 years with 40 females and 20 males. Body mass index was a mean of 28.3. DeMeester score was normal in 12/60 with atypical symptoms and abnormal in the rest. Good correlation was shown between scintigraphy and impedance, manometry and distal pH readings. Pulmonary aspiration was shown in 25/60 (15 with atypical symptoms) and LPR in 20/30. Several impedance, manometric and scintigraphic finding were good predictors of lung aspiration of refluxate.

Conclusion: Scintigraphy provides a good tool for screening patients with typical and atypical symptoms of GORD. It is well correlated with the standard methods for the diagnosis and provides visual evidence of LPR and lung aspiration.

[1]CNI Molecular Imaging & University of Notre Dame, Sydney, Australia
[2]Ryde Medical Centre, Sydney, Australia
[3]Sydney Heartburn Clinic, Concord Hospital & University of Sydney, Sydney, Australia
[4]Brisbane Private Hospital, Brisbane, Australia

Corresponding author:
Hans Van der Wall, Suite 101, 5 Bay Drive, Meadowbank, NSW 2114, Australia.
Email: hvanderwall@gmail.com

Keywords
GORD, scintigraphy, laryngopharyngeal, impedance, pH

Received 24 June 2020; accepted 2 September 2020

Introduction

Chronic diseases are an increasingly prevalent challenge to healthcare systems globally from a financial and societal perspective. This group of diseases are the leading cause of illness and disability, accounting for ~70% of deaths worldwide.[1,2] Global healthcare spending is projected to reach $US10.059 Trillion by 2022, an annual growth rate of 5.4%.[3]

Gastro-oesophageal reflux disease (GORD) is an exemplar of the complexities of chronic disease.[4] The changing epidemiology of the Australian population is associated with an increasing prevalence of GORD and other consequent chronic diseases.[4–6]

Gastro-oesophageal reflux disease is defined as "a condition which develops when reflux of stomach contents causes troublesome symptoms and/or complications".[7] The current diagnostic testing regimen is predicated on acid exposure despite the universal definition being devoid of this term. There is increasing evidence for more complex injury from agents such as pepsin and bile constituents.[5] The focus on typical symptoms of heartburn and regurgitation with the interdependence on acid exposure time (AET) underestimates disease in individuals with atypical symptoms. Diagnostic efficacy is impaired as the symptoms span a multitude of disparate specialities.[8]

The true economic cost of GORD may be approximated from data extracted from the Pharmaceutical Benefits Schedule (PBS) and the Medicare Benefits Schedule (MBS). There has been a reduction in the cost of anti-reflux medications from AUD$500M in 2012–2013 to AUD$264M in 2018–2019.[9,10] Nevertheless, Esomeprazole (Nexium) and Pantoprazole (Somac) are consistently amongst the top 10 most prescribed drugs in Australia.[11] A recent multi-centre trial has reported that that up to 30% of patients may be inappropriately treated with PPIs.[12] Diagnostic procedures for GORD under the MBS increased from AUD$67.2M in 2012–2013 to AUD $80.3 in 2018– 2019.[10]

We hypothesise that a validated simple scintigraphic reflux study can screen for local and extra-oesophageal manifestations of GORD, thereby expediting the diagnosis and reducing costs.

Methods

Population

The two patient groups consisted of consecutive patients referred for laparoscopic fundoplication for failed therapy with proton pump inhibitors (PPIs) or that remained undiagnosed after 8 weeks of investigation and classified according to the reflux symptom index criteria of Belafsky et al.[13] The second group comprised patients with atypical symptoms of GORD presenting to otolaryngologists or other specialists. All patients underwent 24-hour oesophageal impedance/pH/manometry studies. Major symptoms included heartburn, globus and regurgitation or extra-oesophageal symptoms such as cough, sore throat, recurrent throat clearing, voice change, laryngospasm and aspiration. Scintigraphy was used to prospectively evaluate extra-oesophageal refluxate and the possibility of pulmonary aspiration of refluxate. These patients had failed maximal therapy and underwent

these investigations after cessation of PPI therapy. Clinical data and body mass index (BMI) were prospectively collected using a standardized proforma and entered into a database.

24-hour impedance study

Twenty four-hour impedance studies with two channel 24-hour pH was performed on all patients as has been described elsewhere.[14] Briefly, a trans-nasal catheter with 2 level impedance rings and 2 level pH electrodes connected to an external monitoring device was inserted into the oesophagus. Impedance rings were set at 5 and 15 cm above the upper border of the lower oesophageal sphincter (Zephyr device, catheter ZAI-BD31, Sandhill Co, Highlands Ranch, Colorado, USA). Reflux was classified by the consensus on impedance and pH monitoring.[15]

Manometry

Standard stationary manometry was obtained with a water perfused dent sleeve 8 channel catheter (Dent Sleeve International, Mississauga, Ontario, Canada) as described elsewhere.[14] Data was recorded with a multichannel recording system (PC polygraph HR Medtronics, Synectics Medical, Minneapolis, Minnesota, United States) and analysed using the PolyGram software program (Medtronics, Synectics Medical, Minneapolis, Minnesota, United States). Motility was graded by modification of Kahrilas et al. method.[15,16]

Scintigraphy

Patient preparation involved a 6 hour fast and 24-hour cessation of anti-reflux medication prior to the test. The patient was administered a radiopharmaceutical (60–100MBq of 99 m-Tc Phytate) in 50 mL of water followed by a further 50 mL of water to clear the oropharynx and oesophagus. Dynamic images were acquired upright for 2 minutes then supine for 30 minutes on a Hawkeye 4 gamma camera (General Electric, Milwaukee, United States) with the mandible and stomach in the field of view.

Delayed static imaging was obtained 2 hrs later for assessment of lung aspiration of refluxate (Figure 1). Images analysis is shown in Figure 2.

A subgroup of the 30 patients with extra-oesophageal symptoms underwent single photon emission computed tomography (SPECT) which was fused with x-ray computed tomography (CT) on the same instrument (Figure 1).

Statistical analysis

Data was analysed by nonparametric statistical methods as much of the analysis was of ordinal data. Standard ANOVA statistics and 2-tail Spearman (non-parametric data) and Pearson correlation coefficient (parametric data) with significance levels of 0.05 were utilised. Receiver operating characteristic (ROC) analysis was also undertaken where appropriate. Statistica V8 software (Statsoft, Oklahoma, United States) package was used for data analysis.

Results

Population

Sixty consecutive patients (40 M, 20 F) were entered into the database approved by the University of Notre Dame Ethics Committee (No. 015149S). Average age was 55.8 years (Range: 18–87, Median: 58 yrs). Thirty patients gave a history of predominantly atypical symptoms and 28 a history of typical heartburn and regurgitation with overlap in 2.

The BMI in this cohort ranged from 19.8 to 47.9 kg/m^2, with a mean of 28.3 and median of 27.4. Twenty seven of the 60 patients had a BMI in excess of 30.0 kg/

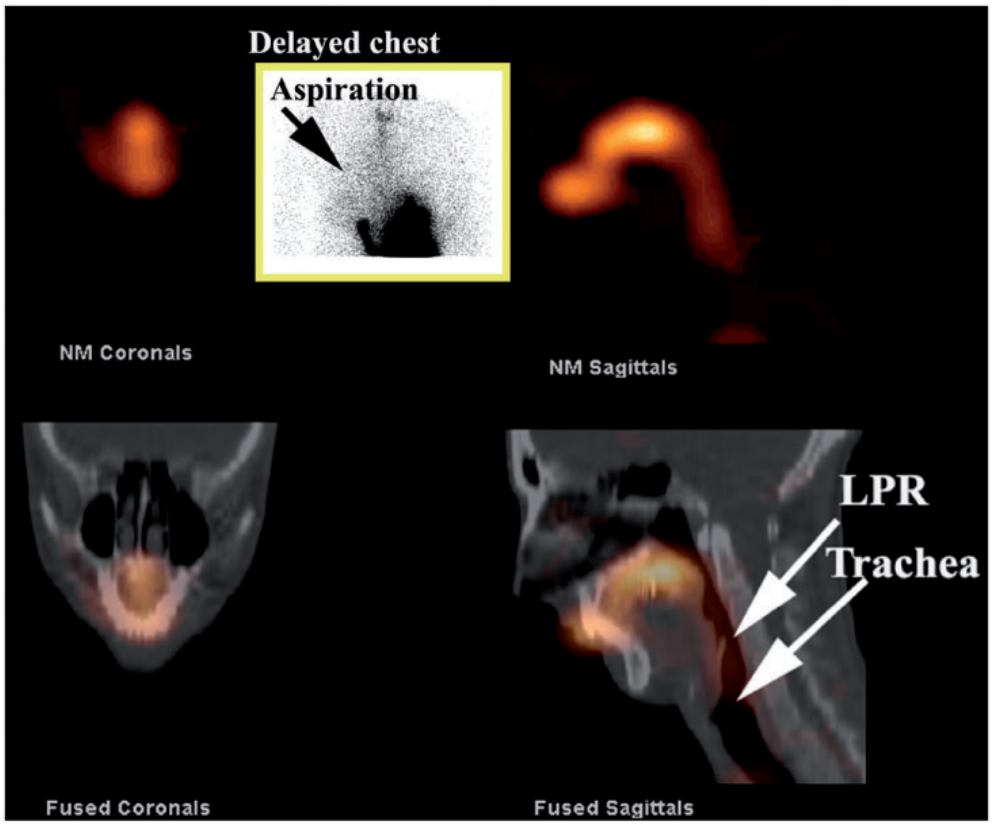


Figure 1. SPECT/CT and delayed image of lungs (inset). The inset image shows a delayed study of the anterior chest at 2 hours. There is aspiration of refluxate into the right lung (arrow). The SPECT/CT image shows the scintigraphic image in the upper panel and the fused image with the CT study in the lower panel. There is significant contamination of the laryngopharynx (LPR) and trachea by refluxate.

m^2 (Normal: 18.5 to 24.9). No patient had a BMI below the normal range.

DeMeester scores: The DeMeester score[17] was normal in 12 of 60 patients, being less than 14.7. These patients were in the group with atypical symptoms.

Hiatus hernias

A hiatus hernia was diagnosed in 24 patients based on endoscopic criteria.

Manometry

Oesophageal motility: Normal oesophageal motility was present in 13 patients. Mild abnormality was found in 9, mild to moderate in 12, moderate in 13 and severe in 13 patients. In the Kahrilas et al.[18] classification system this would have been normal in 22, moderate in 12 and severe in 26 patients.

Mean LOS pressure 6 mm Hg (Range: 0–29, Median: 4). Normal was considered to be above 26 mm Hg.[19] LOS pressure was normal in only 4 patients.

Impedance

The times for impedance to return to its pre-bolus level after a fall during the reflux event are shown in Table 1. Resting impedance is typically $\sim$2200 Ω and falls to $\sim$500 Ω during a reflux event.[20,21] Normal bolus clearance has been reported as less than 5 seconds.[20] Total bolus clearance was abnormal in 48 of the 60 patients.

pH/Impedance

Acid exposure times are shown in Table 2. Thirty eight patients had an acid exposure time in excess of 6.3%.[22] Proximal total

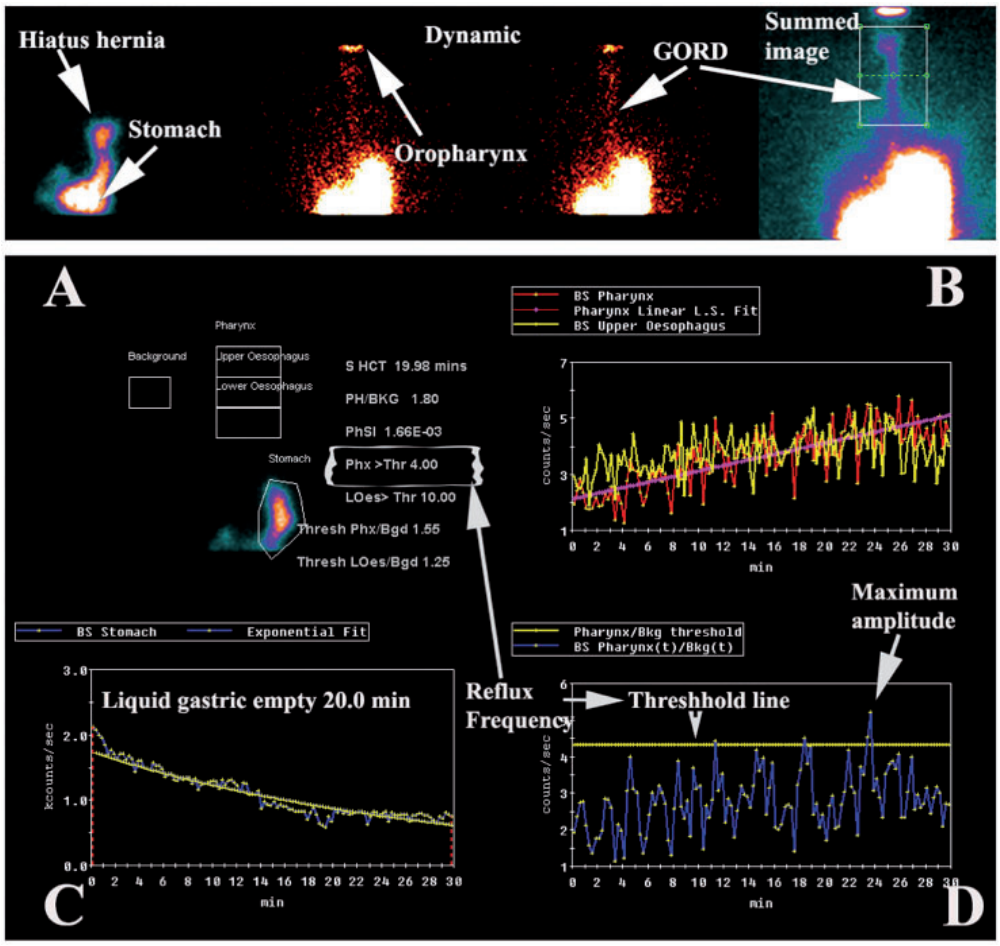


Figure 2. Analysis of the dynamic study. The upper panel shows the dynamic study which allows visualisation of any hiatus hernias and GORD to the level of the pharynx (arrows). The summed dynamic image clearly shows evidence of GORD to the level of the pharynx. The panel below illustrates the analysis of the pattern of reflux in the pharynx/laryngopharynx (upper box) and upper oesophagus (middle box) in A. B shows the pattern of activity in the pharynx/laryngopharynx (red curve with fitted pink line) and oesophagus (yellow curve) over 30 minutes of acquisition. The liquid gastric emptying (C) is calculated by an exponential fit to the activity over the stomach region of interest in A. Frequency and amplitude of reflux is calculated from the pharyngeal/laryngopharyngeal curve in B after taking into account background activity (Threshold line) in D.

Table 1. Impedance: Times for impedance to return to baseline after reflux event.

Bolus clearance (secs)	Mean	Median	Range
Upright	15.6	14.0	0–74.0
Recumbent	16.5	10.0	0–167.0
Total	13.0	10.5	1.0–74.0

Table 2. pH: percentage acid exposure times.

Acid exposure	Mean	Median	Range
Proximal	8.1	6.0	0–46.0
Distal	38.5	30.3	0–56.0

reflux events (acid+non-acid) were a mean of 27.5% in 24 hrs (Median 24.0, Range 2.0–104.0). Normal reflux frequency ($\leq$31 in 24 hrs)[22] of all events (acid and nonacid) was found in 13 patients in the proximal oesophagus. Ten of these 13 patients were in the group of 30 with atypical symptoms in which the scintigraphic studies were abnormal and 3 were in the group

undergoing fundoplication of which 2 showed aspiration of refluxate into the lungs.

Scintigraphy

No scintigraphic evidence of GORD was shown in 12 of the 60 patients. The primary symptom of these 12 patients was chronic cough without heartburn or regurgitation. Scintigraphic parameters are presented in Table 3 The time-activity curve analysis for the pharynx/laryngopharynx and upper oesophagus are presented in Table 4.

The mean liquid gastric emptying time was 20.1 minutes and 23 of the 60 patients were within the normal range (Normal <19 minutes).

Pulmonary Aspiration of refluxate was shown in 25 of 60 patients, with 15 of the 25 giving a history of atypical symptoms.

Table 3. Scintigraphic parameters (n = 60).

Scintigraphy	Mean	Median	Range
Frequency (in 30 min)	14.0	10.0	0–43
Amplitude Ratio	5.5	2.2	0–36
AUC Ratio	2.2	1.9	0–20
Liquid gastric empty (min)	20.1	11.3	15.0–45.5

Table 4. Scintigraphic curve analysis for upper oesophagus and pharynx/laryngopharynx.

Region	Grade 0	Grade 1	Grade 2	Grade 3
Upper Oes Up	12	2	6	21
Upper Oes Sup	12	21	7	20
Pharynx Up	12	13	7	28
Pharynx Sup	12	12	2	34

Statistical comparisons of oesophageal physiology and scintigraphy

All positive correlations between manometry and impedance pH are shown in Table 5. There was no correlation between liquid gastric emptying and any manometric, impedance, pH measures or lung aspiration of refluxate in the scintigraphic studies.

All positive correlations with lung aspiration are shown in Table 6.

If the normal values of proximal reflux events (acid +non-acid) in 24 hr impedance studies were utilised (≤31 events in 24 hours), 2 patients would not have been suspected of reflux with involvement of pulmonary aspiration in the cohort of 30 patients with atypical symptoms.

Table 5. Correlations of manometry and impedance/pH with scintigraphy.

Correlates	Correlation coefficients	p values
Manometric oesophageal motility & rising Scintigraphic curves for pharynx/laryngopharynx & upper oesophagus	Spearman 0.35 (up) 0.61 (sup)	0.02 (up) 0.00 (sup)
Manometric peristalsis & Scintigraphic amplitude of reflux	Pearson 0.48	0.01
Manometric motility & Scintigraphic amplitude (negative correlation – as motility worsened amplitude increased)	Pearson 0.45	0.02
Impedance/pH All recumbent reflux events (acid +non-acid) & Scintigraphic reflux frequency for the laryngo-pharynx/pharynx	Pearson 0.50	0.00
Impedance/pH All distal reflux events (acid+non-acid) & Scintigraphic reflux frequency for laryngopharynx/ pharynx	Pearson 0.17	0.03

Table 6. Correlations with lung aspiration in the scintigraphic study.

Correlates	Correlation coefficients	p values
Manometric oesophageal motility & aspiration	Spearman 0.72	0.00
Impedance Total bolus clearance & aspiration	Spearman 0.63	0.00
Impedance/pH All reflux events (acid+non-acid) & aspiration	Spearman 0.45	0.04
Scintigraphic Rising pharyngeal/oesophageal curves & aspiration	Spearman 0.41 (up) 0.38 (sup)	0.04 (up) 0.00 (sup)

No acid reflux event in the distal or proximal oesophagus had a significant relationship with lung aspiration.

SPECT/CT

The 30 patients who underwent SPECT/CT studies of the head and neck showed refluxate contamination of the larynx and pharynx (LPR) and nasopharyngeal reflux in 20 cases. Eight of these patients demonstrated maxillary sinus contamination by refluxate and CT evidence of soft tissue disease in the sinuses. Middle ear contamination was seen in 2 patients. Moderate correlation was demonstrated between LPR/nasopharyngeal contamination of refluxate in the SPECT/CT studies and lung aspiration (Spearman correl coeff $=0.36$, $p = 0.04$)

The receiver operating characteristic (ROC) curve analysis illustrates Total bolus clearance, oesophageal motility, scintigraphic pharyngeal upright and supine curves and ratio of area under the curve for pharynx to background to be the best predictors of pulmonary aspiration of reflux. (Figure 3).

Discussion

The patients in this study illustrate a mixture of the extreme end of the GORD spectrum or with atypical symptoms such as chronic cough. It reflects the complexity and heterogeneity of disease processes under the diagnostic umbrella of GORD. The incidence of GORD is growing across the Australian population up to the age of 70 years, with the greatest increase in the 30 to 39 year age bracket.[6] This adds to the burden of disease with 50% of Australians affected by one and 23% affected by two or more chronic conditions.[1,23]

The diagnostic algorithm for GORD in the presence of heartburn and regurgitation is established and validated.[24] The hierarchical diagnostic model[25] involves a PPI trial in patients whose symptoms are refractory and gastroscopy to exclude oesophagitis or other sinister pathology.[24,26,27] Endoscopy has a low diagnostic accuracy for detection of GORD with questionable utility as 50–70% of patients will have a normal study.[4,25,28] Next in the sequence is oesophageal pH/impedance/manometry testing.[24,26] This diagnostic model is suitable for local oesophageal disease but sensitivity and specificity diminish with extra-oesophageal symptoms.[5,27] It is in this group that the complexity of the medical response proliferates with an associated escalation in cost. A shift in the anatomical geography of the disease invokes referrals to otolaryngoligists, respiratory physicians and others. GORD then transmutes into a new lexicon with terms such as "laryngopharyngeal reflux" and "airways reflux". While 24-hour oesophageal impedance/pH monitoring with pharyngeal probes has shown promise, its reproducibility for predicting LPR has been questioned and remains an indirect investigational technique for pharyngeal or pulmonary exposure to refluxate.[29]

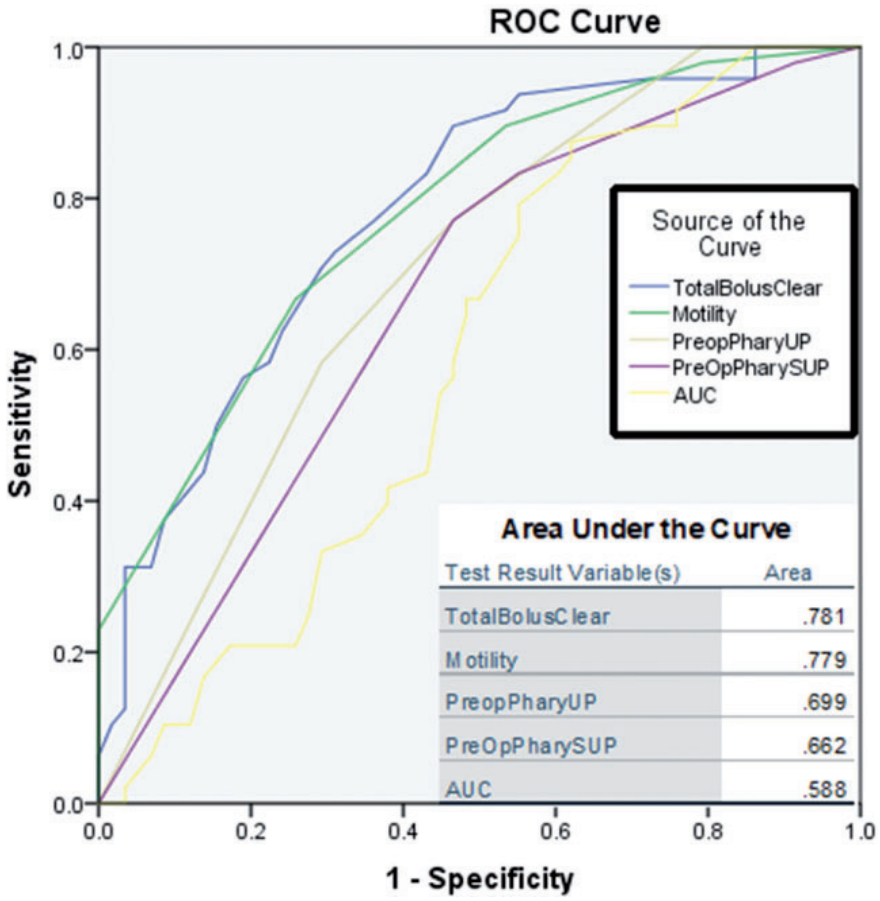


Figure 3. ROC curve for the best predictors of aspiration of refluxate into the lungs. Total bolus clearance by impedance and oesophageal motility are the best predictors of aspiration of refluxate into the lungs.

The scintigraphic test integrates the diagnosis of oesophageal and extra-oesophageal disease by direct visualisation of refluxate at these sites. It has been validated against the current standards for detecting GORD[14,30] and is endorsed by Medicare.

There is a notional belief that the fundamental pathophysiology of gastro-oesophageal reflux disease is acid in spite of evidence to the contrary.[5,31] Consequently, individuals with atypical or silent reflux are relegated to alternative pathways and the risk of further chronic diseases such as pulmonary infection and fibrosis.[32] This problem is well illustrated by the cohort in this study in which 30 of 60 patients gave an atypical history of GORD. Many of these patients had normal DeMeester scores and although the mean acid exposure was 8.1%, only 38% had pH exposure above the normal cut-off level of 6.3%.[22] The preoccupation with acid exposure time(AET) is illustrated by the disparity between the distal and proximal acid exposures with a majority having significant acid exposure distally (Mean 38.5, Median 30.3, Range 0–56.0%) and only 12% recording a proximal acid exposure ($pH < 4.0$) above 1.2%.[33] There is limited veracity in the quality of data regarding proximal AET due to variability in electrode placement.[29,33,34] It suggests significant neutralisation of acid in ascent, gaseous reflux or predominantly low-grade reflux that does not reach the proximal oesophagus.[35] The impedance data favours the former explanation as total proximal reflux (acid + non-acid) greater than 31 episodes in 24 hours[22] was recorded in 68%. These finding confirm previous work pertaining to the

short-comings of oesophageal pH monitoring.[36] The atypical patient group may also help to explain the normality of the DeMeester scores in 12 of 30, a finding resulting from non-acid reflux events that has been reported by others.[36]

Dissecting the costs involved in the detection and treatment of GORD in the Australian Healthcare system is problematic. Estimates of the prevalence are based on the typical symptoms of heartburn and regurgitation and exclude atypical symptoms.[24,37]

The MBS and PBS provide the quantity and cost of GORD in the Australian population utilising publicly available Government data. There has been a marked fall in the number of prescriptions for anti-reflux medications with a disproportionate fall in the costs involved. (Figure 4) This variation is attributed to a series of factors:

1. rescheduling (prescription to over-the-counter availability).[38–41]
2. expiry of drug patents, resulting in a decrease in cost.[38–41]
3. a global shift from PPI use. The frequency of reported side-effects has been questioned, but caution in long-term PPI use has been recommended.[42]

There has been an increase in quantity and cost of diagnostic procedures from 2012–2019 (Figure 5). The increase signifies the diagnostic justification of GORD within an individual[4] as recommended in Bettering the Evaluation and Care of Health (BEACH) program in 2014.[43] Gastroscopy accounts for 84% of diagnostic expenditure despite questionable diagnostic accuracy in GORD.[28]

The cost and quantity of surgical procedures have followed an incremental uniform increase over the period. Figure 6 illustrates surgical procedures over the period. Endoscopic dilatation has been excluded due to the changed classification under Medicare.

Gross data suggests an increased prevalence of GORD. Co-morbidities that increase the prevalence of GORD include older age, male sex, race, analgesic consumption, consumption of alcohol, smoking and BMI in conjunction with numerous other lifestyle related factors.[6,44–46] Worryingly, 67% of the Australian population is overweight or obese. Coincidently, there has been a rise in diabetes mellitus from

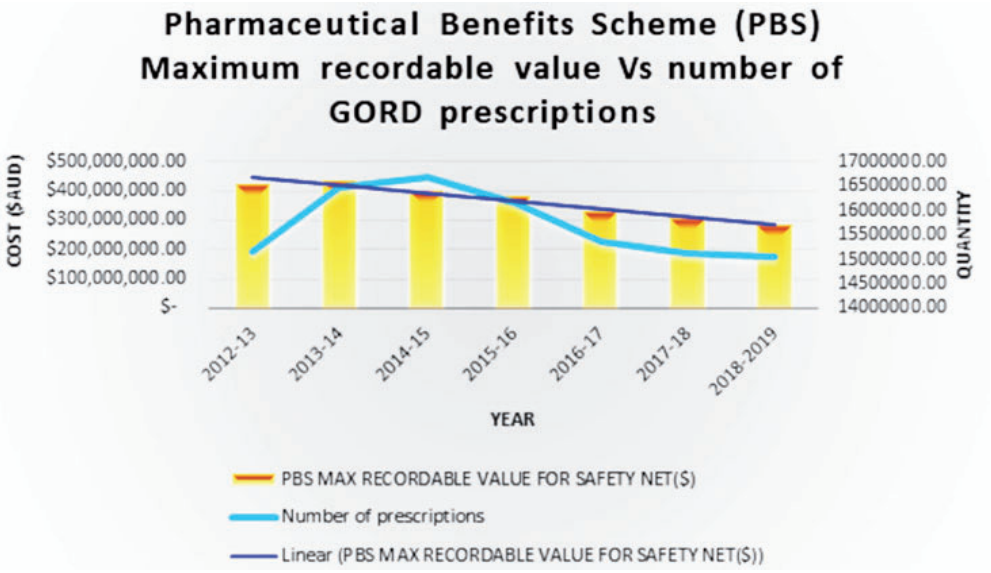


Figure 4. Data derived from Pharmaceutical Benefits Schedule (PBS) 2012–2019.[9,10]

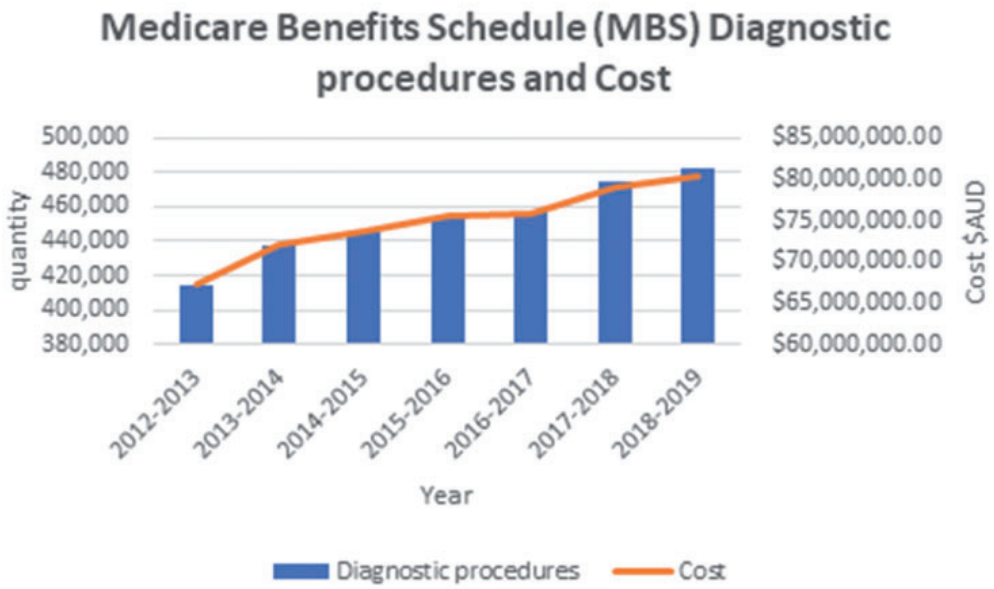


Figure 5. Data derived from the Medicare Benefits Schedule (MBS) 2012–2019.[9,48]

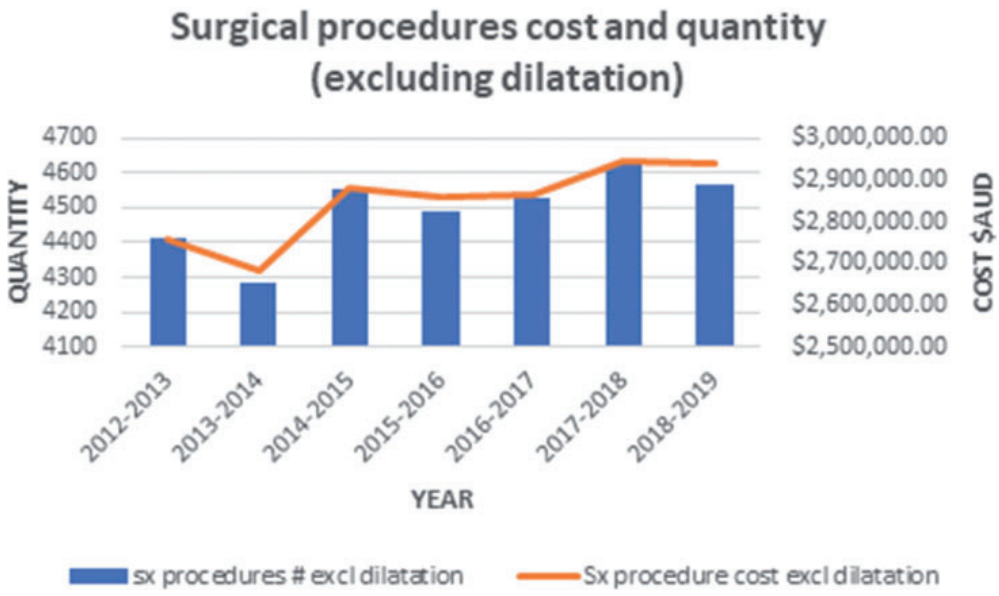


Figure 6. Data extracted from Medicare Benefits Schedule 2012–2019.[9,48]

approximately 1 to 4% between 1995 and 2018. Central abdominal obesity increases the risk of Barrett's oesophagus, oesophageal adenocarcinoma, elevates intra-abdominal pressure promoting reflux and development of hiatus hernia.[44–46]

While this data illustrates the societal and financial burden imparted by GORD, it also underlines manifold deficiencies in data collection in Australia. Data is collected via self-reporting, which is unreliable, inaccurate and has poor reproducibility.[47] Historical data is limited as GORD was consolidated under the umbrella of digestive diseases until 2014. Calculating the true burden of disease is further

complicated by records held across multiple disparate databases.

Conclusion

Chronic diseases are the greatest challenge confronting the Australian health care system. GORD is a chronic disease with an increasing prevalence. A new diagnostic/therapeutic algorithm must be implemented, especially in the setting of atypical GORD. This is reinforced by increasing adverse reports on the side effects of PPIs. Nuclear scintigraphy provides an innovative approach, which optimises diagnosis in the setting of typical and atypical GORD. This offers an early and cost-effective diagnostic window that allows disease prevention and risk factor management.

Acknowledgements

NA

Contributorship

Burton, Leticia: Idea, design and writing. Beattie, John: Manuscript review, contribution of patients. Falk, Gregory: Manuscript review, contribution of patients. Hans Van der Wall: Design and statistics and manuscript review. William Coman: Manuscript review and Ideas.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

Ethical approval to report this series was obtained from University of Notre Dame, Sydney Campus (No. 015149S).

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Guarantor

Leticia Burton.

Informed consent

Written informed consent was obtained from the patient(s) for their anonymised information to be published in this article.

ORCID iD

Hans Van der Wall https://orcid.org/0000-0003-4184-3330

References

1. Australian Government. *National strategic framework for chronic conditions*. Canberra, ACT, Australia: Department of Health and Ageing, 2017.
2. Australian Institute of Health and Welfare. *Australia's health 2018. Australia's health series no. 16*. Canberra, ACT, Australia: Australian Institute of Health and Welfare, 2018.
3. Deloitte-Touche-Tohmatsu. *2019 Global health care outlook. Shaping the future*. UK: Deloitte-Touche-Tohmatsu, 2019.
4. Naik RD and Vaezi MF. Recent advances in diagnostic testing for gastroesophageal reflux disease. *Expert Rev Gastroenterol Hepatol* 2017; 11: 531–537.
5. Gyawali C, Kahrilas P, Savarino E, et al. Modern diagnosis of GERD: the Lyon Consensus. *Gut* 2018; 67: 1351–1362.
6. Yamasaki T, Hemond C, Eisa M, et al. The changing epidemiology of gastroesophageal reflux disease: are patients getting younger? *J Neurogastroenterol Motil* 2018; 24: 559–569.
7. Vakil N, van Zanten SV, Kahrilas P, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; 101: 1900–1920; quiz 1943.
8. Pacheco-Galvan A, Hart SP and Morice AH. Relationship between gastro-oesophageal reflux and airway diseases: the airway reflux paradigm. *Arch Bronconeumol* 2011; 47: 195–203.
9. Government A. *Pharmaceutical benefits schedule item reports*. Canberra, ACT:

Services Department of Health and Ageing, 2012–2019.
10. Australian Government. *Schedule of pharmaceutical benefits*. Canberra, ACT: Department of Health and Ageing, 1992–2019.
11. MedicineWise. Top 10 drugs 2018–19. *Aust Prescriber* 2019; 42: 204.
12. Spechler SJ, Hunter JG, Jones KM, et al. Randomized trial of medical versus surgical treatment for refractory heartburn. *N Engl J Med* 2019; 381: 1513–1523.
13. Belafsky PC, Postma GN and Koufman JA. Validity and reliability of the reflux symptom index (RSI). *J Voice* 2002; 16: 274–277.
14. Falk GL, Beattie J, Ing A, et al. Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? *World J Gastroenterol* 2015; 21: 3619–3627.
15. Kahrilas PJ, Dodds WJ, Hogan WJ, et al. Esophageal peristaltic dysfunction in peptic esophagitis. *Gastroenterology* 1986; 91: 897–904.
16. Kahrilas PJ, Dent J, Dodds WJ, et al. A method for continuous monitoring of upper esophageal sphincter pressure. *Dig Dis Sci* 1987; 32: 121–128.
17. Johnson L and DeMeester T. Twenty-four hour pH monitoring of distal esophagus. A quantitative measure of gastro-esophageal reflux. *Am J Gastroenterol* 1974; 62: 325–332.
18. Kahrilas PJ, Clouse RE and Hogan WJ. American gastroenterological association technical review on the clinical use of esophageal manometry. *Gastroenterology* 1994; 107: 1865–1884.
19. Richter JE, Wu WC, Johns DN, et al. Esophageal manometry in 95 healthy adult volunteers. Variability of pressures with age and frequency of "abnormal" contractions. *Dig Dis Sci* 1987; 32: 583–592.
20. Imam H, Shay S, Ali A, et al. Bolus transit patterns in healthy subjects: a study using simultaneous impedance monitoring, videoesophagram, and esophageal manometry. *Am J Physiol Gastrointest Liver Physiol* 2005; 288: G1000–G1006.
21. Sifrim D, Castell D, Dent J, et al. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. *Gut* 2004; 53: 1024–1031.
22. Shay S, Tutuian R, Sifrim D, et al. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: a multicenter report of normal values from 60 healthy volunteers. *Am J Gastroenterology* 2004; 99: 1037–1043.
23. *Australia's health 2018*. Canberra, ACT, Australia: Department of Health and Ageing, 2018.
24. Katz PO, Gerson LB and Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013; 108: 308–328; quiz 329.
25. Savarino E, Bredenoord AJ, Fox M, et al. Advances in the physiological assessment and diagnosis of GERD. *Nat Rev Gastroenterol Hepatol* 2018; 15: 323–304.
26. Richter JE. How to manage refractory GERD. *Nat Clin Pract Gastroenterol Hepatol* 2007; 4: 658–664.
27. Richter JE. Current diagnosis and management of suspected reflux symptoms refractory to proton pump inhibitor therapy. *Gastroenterol Hepatol* 2014; 10: ■.
28. Hatlebakk JG. Endoscopy in gastro-oesophageal reflux disease. *Best Pract Res Clin Gastroenterol* 2010; 24: 775–786.
29. Zerbib F, Roman S, Bruley Des Varannes S, et al. Normal values of pharyngeal and esophageal 24-hour pH impedance in individuals on and off therapy and interobserver reproducibility. *Clin Gastroenterol Hepatol* 2013; 11: 366–372.
30. Burton L, Falk GL, Parsons S, et al. Benchmarking of a simple scintigraphic test for gastro-oesophageal reflux disease that assesses oesophageal disease and its pulmonary complications. *Mol Imaging Radionucl Ther* 2018; 27: 113–120. 2018/10/16. DOI: 10.4274/mirt.10438.
31. Usai Satta P, Oppia F and Cabras F. Overview of pathophysiological features of GERD. *Minerva Gastroenterol Dietol* 2017; 63: 184–197.
32. Morice A. Airway reflux as a cause of respiratory disease. *Breathe* 2013; 9: 256–266.
33. Ayazi S, Hagen JA, Zehetner J, et al. Proximal esophageal pH monitoring: improved definition of normal values and

determination of a composite pH score. *J Am Coll Surg* 2010; 210: 345–350.
34. Kawamura O, Aslam M, Rittmann T, et al. Physical and pH properties of gastroesophagopharyngeal refluxate: a 24-hour simultaneous ambulatory impedance and pH monitoring study. *Am J Gastroenterology* 2004; 99: 1000–1010.
35. Mainie I, Agrawal A, Tutuian R, et al. The role of proximal pH monitoring. *Am J Gastroenterol* 2005; 100: 1621–1622.
36. Mainie I, Tutuian R and Castell DO. The limitations of pH monitoring for detecting gastroesophageal reflux. *Clin Gastroenterol Hepatol* 2006; 4: 1184; author reply 1185.
37. El-Serag HB, Sweet S, Winchester CC, et al. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2014; 63: 871–880.
38. Australian Government. *The impact of PBS reform*. ACT, Australia: Department of Health and Ageing, 2010, pp.1–117.
39. Australian Government. *Scheduling delegate's final decisions*. Canberra, ACT, Australia: Australian Government, 2016 (press release).
40. Australian Government. *Scheduling delegate's final decisions*. Canberra, ACT, Australia: Australian Government, 2017 (press release).
41. Australian Institute of Health and Welfare. *Impact of overweight and obesity as a risk factor for chronic conditions*. Australian Burden of disease study. Canberra, ACT, Australia: Australian Institute of Health and Welfare, 2017.
42. Yadlapati R and Kahrilas PJ. The "dangers" of chronic proton pump inhibitor use. *J Allergy Clin Immunol* 2018; 141: 79–81.
43. Miller G, Wong C and Pollack A. Gastro-oesophageal reflux disease (GORD) in Australian general practice patients. *Aust Fam Physician* 2015; 44: 701–704.
44. Boeckxstaens G, El-Serag HB, Smout AJPM, et al. Symptomatic reflux disease: the present, the past and the future. *Gut* 2014; 63: 1185–1193.
45. Kim KJ and Lee BS. Central obesity as a risk factor for Non-Erosive reflux disease. *Yonsei Med J* 2017; 58: 743–748.
46. Corley DA, Kubo A and Zhao W. Abdominal obesity, ethnicity and gastro-oesophageal reflux symptoms. *Gut* 2007; 56: 756–762.
47. Bhandari A and Wagner T. Self-reported utilization of health care services: improving measurement and accuracy. *Med Care Res Rev* 2006; 63: 217–235.
48. Australian Government. *Medicare item reports*. Canberra, ACT, Australia: Department of Health, 1992–2019.

Received: 6 August 2020 | Accepted: 4 November 2020

DOI: 10.1111/cpf.12677

ORIGINAL ARTICLE

Clinical Physiology and Functional Imaging

A transformational change in scintigraphic gastroesophageal reflux studies: A comparison with historic techniques

Leticia Burton[1] | David Joffe[2] | Douglas W Mackey[1] | Hans Van der Wall[1] | Gregory L Falk[3]

[1]CNI Molecular Imaging & University of Notre Dame, Sydney, NSW, Australia

[2]Department of Respiratory Medicine, Royal North Shore Hospital, Sydney, NSW, Australia

[3]Sydney Heartburn Clinic, Concord Hospital & University of Sydney, Sydney, NSW, Australia

Correspondence
Leticia Burton, CNI Molecular Imaging, Suite 101/5 Bay Dr, Meadowbank, NSW 2114, Australia.
Email: leticia.burton@gmail.com

Abstract

Background: The inclusion of scintigraphy in the diagnostic algorithm for gastroesophageal reflux is controversial due to variability in methodology and reporting. A novel scintigraphic reflux study has been developed and validated against the current standards for the diagnosis of gastroesophageal reflux disease (GORD).

Objective: To compare a new scintigraphic reflux test against historic techniques and standardised diagnostic reference tests for gastroesophageal reflux disease.

Methods: Paired scintigraphic studies were conducted in seventeen patients. All patients underwent at least one other standardised diagnostic reflux test such as 24- hour oesophageal impedance/ pH, and oesophageal manometry, barium swallow, gastroscopy or the Peptest. Patients inadvertently presented at sites B for scintigraphic reflux testing rather than at Site A which was part of an approved study. The findings from sites B did not correlate with clinical symptoms and other diagnostic reference tests from GORD. These studies were then repeated at Site A with approval from the patients. A second reflux study was performed at site A, utilising a novel technique with the capability of assessing oesophageal and extra-oesophageal disease.

Results: The Site A technique shows good concordance with the reference diagnostic tests with an accuracy of 82.4% and kappa of 0.64 (SE: 0.16, $p = 0.00$). Site B had an overall accuracy of 47.1% and kappa of 0.066 (SE: 0.068, $p = 0.45$).

Conclusion: The Site A technique shows higher accuracy than either site B or the historic reflux techniques. It has characteristics that make it an effective screening tool for assessment of local oesophageal disease and its extraoesophageal manifestations.

KEYWORDS

adult, aspiration, gastric emptying, gastroesophageal reflux disease, paediatric, scintigraphy

1 | INTRODUCTION

Gastroesophageal reflux disease (GORD) is common and affects up to 30% of individuals globally (Yamasaki et al., 2018). The typical symptoms of heartburn and regurgitation are well documented and treated. Acid suppression therapy is the first line of diagnosis and treatment, with 60%–90% of individuals experiencing a reduction in symptoms (Richter, 2014). In individuals whose symptoms

remain refractory, a hierarchical diagnostic algorithm is instituted, gastroscopy to rule out sinister pathology, followed by 24-hr oesophageal pH/impedance, manometry and where warranted, barium swallow (Richter, 2014; Savarino et al., 2018). Historically, scintigraphy has not been incorporated into this algorithm as the techniques have been found to lack sensitivity and reproducibility (Shay et al., 1992).

The rationale for exclusion of scintigraphy in the past has been significant variability in technique, reporting and reproducibility (Kjellen et al., 1991; Shay et al., 1992). This belief is based upon early reports of a lack of sensitivity, based on several studies dating back to the 1970s and 1980s, where predominantly visual analysis rather than computerized region of interest analysis was utilized. Molecular imaging has been transformed by the initiation of multiple technological advances incorporated with a growing knowledge of the pathophysiology of GORD in the past 10–15 years. In particular, the instrumentation has evolved to a level where most of the devices available since the early 2000s were hybrid composites of fast gamma cameras and X-ray computed tomography (CT) together with powerful and flexible computerized software. These developments have been incorporated into the scintigraphic reflux techniques at Site A and integrated with the advances in the field of gastroenterology, otolaryngology and respiratory medicine. Most notably, many of these changes are in line with the Montréal and Lyon consensus of GORD. The Montréal consensus is a universal definition of GORD, which acknowledged extraoesophageal symptoms and manifestations (Vakil et al., 2006). Changes in the technology of molecular imaging have allowed the acquisition of fast dynamic studies at the level of the oesophagus and allowed quantitation by region of interest (ROI) analysis, which enhances intra- and inter-observer agreement (Caglar et al., 2003). The addition of CT to the rapid acquisition of single-photon emission computed tomography (SPECT) has allowed direct visualization of refluxate in the head, neck and lungs, regardless of its pH, purely as a physical manifestation.

Scintigraphy evaluates physiologic, metabolic and molecular change or alteration within an individual without altering its existing function (Elgazzar, 2011). This is achieved via careful selection of the radiopharmaceutical (Vallabhajosula et al., 2010) and the use of trace doses of isotope that do not overwhelm the physiology of the system under study. Experimental modelling has demonstrated that as little as 1% of tracer activity in the stomach may be detected in the oesophagus (Caglar et al., 2003).

Site A has assessed the strengths and limitations of the current suite of tests and the previous historical scintigraphic techniques. The primary aim of the new scintigraphic technique is to complement and add value in the diagnosis and management of gastroesophageal and extraoesophageal reflux disease. Quantitation is applied to the oesophagus to derive information pertaining to frequency, amplitude and retention of refluxate in the oesophagus. The technique is not limited by the constraints of instrumentation involved in oesophageal pH, impedance and manometric monitoring. It is better tolerated, and the results in the oesophagus have significant correlation with the current reference standards of oesophageal monitoring with pH/impedance and manometry. However, when a simple lateral image of the delayed study is added, it allows visualization of laryngopharyngeal refluxate and this is even more evident in the SPECT/CT studies.

The technique at Site A has been validated against the current standards for testing of GORD and shown good correlation with pH/impedance and manometry (Burton et al., 2018, 2020; Falk et al., 2015) and for the first time, allowed the direct visualization of refluxate at extraoesophageal sites with SPECT/CT imaging.

We hypothesize that the scintigraphic reflux study implemented at Site A will provide a more sensitive, accurate and reproducible diagnosis of GORD, especially at extraoesophageal sites than the historically based scintigraphic techniques. The opportunity to test this hypothesis was afforded by the implementation of an ethics-approved study comparing the new scintigraphic technique against standard testing for GORD (pH/impedance, manometry and gastroscopy). Several patients inadvertently presented for the scintigraphic

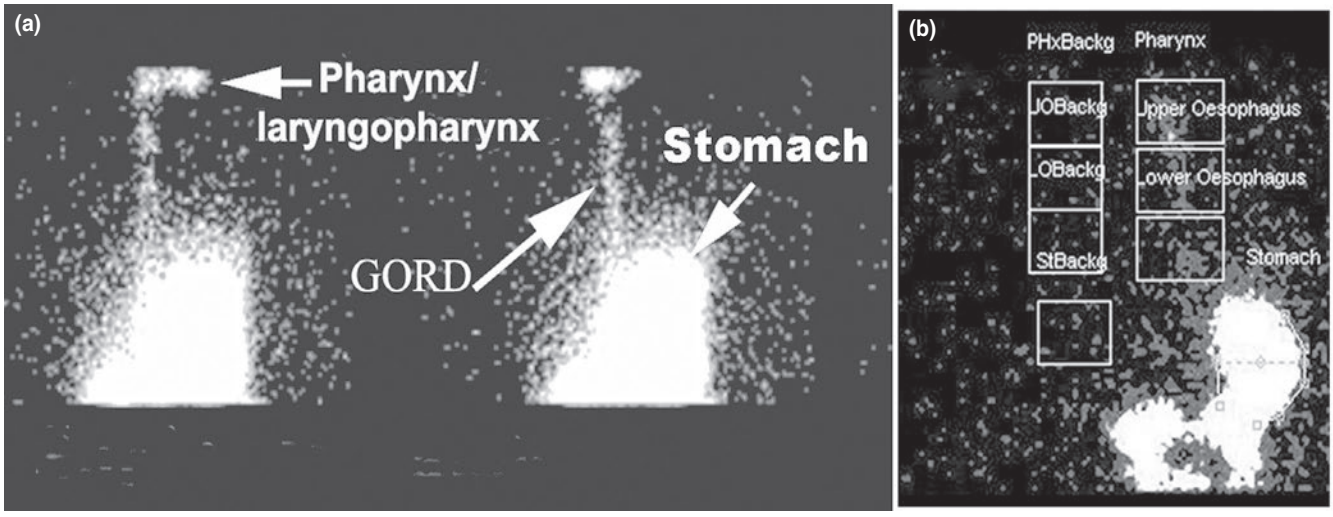


FIGURE 1 Supine dynamic study Site A. The dynamic study demonstrates several frames from a supine study which clearly show the pharynx/laryngopharynx and stomach and the full column of gastroesophageal reflux disease (GORD)

study to multiple other practices using the historic scintigraphic techniques of the past. These patients were subsequently re-studied at Site A as part of the planned study.

2 | METHODS

2.1 | Scintigraphic method at Site A

Patient preparation involved was a minimum 4-hr fast prior to the scan. A dose of 60–100MBq of Technetium-99m (^{99m}Tc) calcium phytate was administered in 150–200 ml of water. All images were acquired on a General Electric Hawkeye 4 Hybrid gamma camera (General Electric). Dynamic images were immediately acquired upright for 2 min followed by supine images at a frame rate of 15 s per frame for a period of 30 min (Figure 1a). The patient continued to fast. Delayed imaging was undertaken at 2 hr post administration of tracer. The delayed imaging involved static images of the lungs and SPECT/CT of the head and neck to evaluate laryngopharyngeal contamination by refluxate in those with a history of atypical symptoms.

All images were qualitatively assessed initially. Quantitative analysis was applied to the dynamic images in the form of regions of interest (ROI) from the laryngopharynx to lower oesophagus and several matching background regions (Figure 1b). Background corrected time–activity curves were derived from each region (Figure 2). Liquid gastric imaging was quantitatively assessed by the geometric mean of the anterior and posterior images in a supine position. Semi-quantitation was applied to the delayed lung image to ascertain evidence of lung aspiration by a line profile, where activity in the main airways was at least twice background (Falk et al., 2015). SPECT/CT was assessed using a binary method as positive or negative for laryngopharyngeal reflux.

2.2 | Scintigraphic method at independent site B

Twelve independent sites constituted Site B, various historic scintigraphic techniques were employed across these sites, with the rationale of evaluating evidence of gastroesophageal reflux. These sites were not direct participants in the research study. The

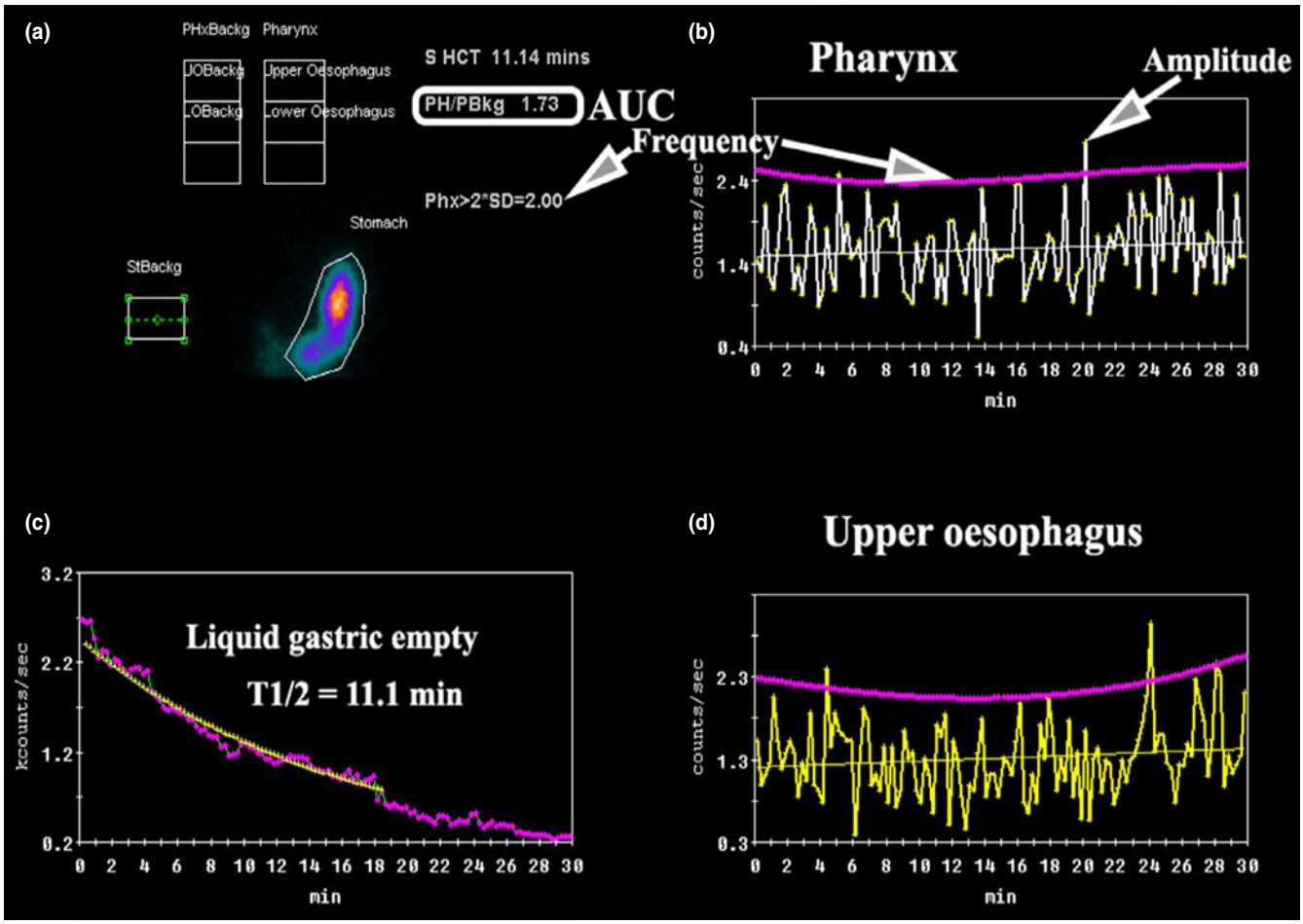


FIGURE 2 Time–activity curve analysis Site A. The four panels in this study demonstrate placement of the regions of interest and background activity in panel a. A number of variables are also provided in this panel including the area under the curve (AUC) ratio for pharynx/laryngopharynx to background which provides an estimate of the rate of clearance of refluxate from the region. Panel b shows the rising time–activity curves for the pharynx/laryngopharynx (red) with the fitted curve to this tracing (pink curve with arrow). Amplitude and frequency of reflux are illustrated. Panel c shows calculation of liquid gastric emptying time to half clearance. Panel d demonstrates the time activity curve for the upper oesophagus.

methodology of studies undertaken at Site B can be broadly categorize into (i) gastroesophageal reflux (ii) combined oesophageal transit and gastroesophageal reflux study.

The fasting period was not stated in any of the reports from the Site B. The various methodologies employed are described in Table 1.

The combined oesophageal transit and gastroesophageal reflux studies were performed in three phases. The methodology for evaluation of purely gastroesophageal was performed in 1, 2 and 3 phases dependent upon the specific site.

Images were qualitatively assessed for reflux and/or transit in all methods. Quantitative analysis was performed in six of the 17. Only four of the 17 studies used the quantitative method of region of interest analysis with generation of time–activity curves.

2.3 | Statistical analysis

Demographic data and the results of the scintigraphic studies were analysed by the ANOVA module in the Statistical Package for the Social Sciences (SPSS) version 24.0 (IBM). Cohen's kappa statistic (Cohen, 1960) was used to compare reproducibility of the scintigraphic tests from the descriptive module of SPSS.

2.4 | Ethical considerations

The study was approved by the Institutional Ethics Committee of the University of Notre Dame, Sydney, Australia (Reference number 015149S) and was performed in line with the principles of the Declaration of Helsinki.

All patients provided written informed consent at Site A, and the reports of previous scans performed at Site B were provided by the patient to compare the finding and correlate with patient history. Studies done at the Site B practices were performed when patients inadvertently presented for the test as part of the prospective arm of the study to alternative practices. A variety of protocols were adopted on an ad hoc basis.

Calcium phytate was used under label for the purpose of gastroesophageal reflux and gastric imaging studies. This was specifically addressed in the ethics approval for this study.

The additional radiation burden associated with SPECT/CT was justified in the presence of atypical symptomology including atypical cough, vocal change and throat clearing. Low-dose CT was utilized in such cases in order to accurately localize refluxate in the head and neck structures.

3 | RESULTS

3.1 | Demographics

Patients had a mean age of 53 years (median 52.5 years, range: 26–77 years) with 10 females and seven males in the cohort. All patients gave a history of either heartburn, regurgitation, chronic cough or throat clearing. Three of the patients were being assessed following laparoscopic fundoplication as part of a prospective study to assess the success of surgery. One of these patients had major recurrent symptoms, and the other two had minor recurrent symptoms.

Most patients in this study had a high pretest probability of gastroesophageal disease as many were being considered for laparoscopic fundoplication and were part of the approved study.

3.2 | Reflux symptom index (RSI)

The mean of the RSI was 24.7 with a median of 25.9. Only one postoperative patient had an RSI score under 13 and the sores ranged from 12 to 36.

3.3 | Reference testing

The 17 patients underwent a combination of 24-hr oesophageal impedance/pH, manometry, gastroscopy and barium swallow. Abnormality for the purpose of the current analysis was predicated on positive findings in any one of these modalities. Two patients were reported as showing no evidence of gastroesophageal reflux by these criteria, although symptomatic.

Mean lower oesophageal sphincter pressure on manometry was abnormal (<6 mm Hg) in 10/12 patients. Normal was considered as 18–23 mm Hg (Tutuian et al., 2003). Barrett's oesophagus was present in four out of five based on endoscopy findings. Oesophageal impedance/pH was abnormal in six of nine patients with three being unable to tolerate the test. Two patients had abnormal barium swallows.

3.4 | Test Site A

All 17 patients were reported as showing gastroesophageal reflux while upright and supine.

Mean amplitude of reflux was 4.1 times background (SD1.7, range 1.5–8.0). The mean ratio of area under the curve for the laryngopharynx to background when supine was 1.5 (*SD* 0.6, Range 0.7–2.5). The frequency of reflux to the pharynx when supine was a mean of 2.9 episodes in 30 min (*SD* 1.3, range 1–6).

Liquid gastric emptying mean half-time was 28.1 min (*SD* 23.6, median 19.9, range 4.1–84.5). Of these 9/17 had normal gastric emptying studies (<19 min) (Camilleri, 2015; Ziessman et al., 2009).

Pharyngeal curves showed a rising pattern in 9/17 patients when upright and in 10/17 when supine.

SPECT/CT showed laryngopharyngeal reflux in nine of nine patients who underwent the study including the post fundoplication patient with major symptoms (heartburn, regurgitation, throat clearing and voice change). SPECT/CT studies were only acquired in

patients with a history of atypical symptoms (mainly recurrent sore throats, throat clearing, recumbent cough or aspiration) in line with radiation-safety principles.

Aspiration of refluxate into the lungs was apparent in 7/17 cases.

3.5 | Statistical considerations

The results from Site A demonstrate an accuracy of 82.4% when correlated with the reference testing for the diagnosis of gastroesophageal reflux and its extraoesophageal manifestations. The kappa value for agreement with the reference tests was good at 0.64 (*SE*: 0.16, $p = .00$), indicating a greater than chance probability of agreement between the tests.

3.6 | Test site B

Six patients were reported as having upright gastroesophageal reflux which did not pass the mid-oesophagus in three cases. One patient was reported as having reflux to the upper oesophagus when supine. One case reported as having no reflux also showed no reflux by the reference testing.

Four of 17 studies were semi-quantitated (Figures 3 and 4). One was reported with a diagnosis of gastroesophageal reflux which was in concordance with the reference standards. The other three were reported as showing no reflux.

Liquid gastric emptying was attempted at three sites with abnormality in two patients and one being calculated by a linear fit to the data, rather than an exponential fit (Ziessman et al., 2009).

No patient was diagnosed with laryngopharyngeal reflux by these methods. One of 13 cases was reported as showing aspiration which was also positive at Site A (Figures 5 and 6). The other 12 patients were reported as showing no pulmonary aspiration, and this was in agreement with Site A for eight cases.

3.7 | Statistical considerations

Considering all scintigraphic reports as positive for reflux plus the one patient with no reflux gives Site B an accuracy of 47.1% for the diagnosis or exclusion of gastroesophageal reflux. The kappa value for agreement with the reference tests is 0.066, which is non-significant (*SE*: 0.068, $p = .45$), indicating a low probability of agreement between the tests.

Accuracy was determined based upon correlation with the suite of standard reference testing.

4 | DISCUSSION

This study demonstrates that Site B instituted historical protocols which were developed for use in the paediatric population. The application of such protocols in the adult population has hindered the ability to answer the diagnostic question due to the inherent differences in anatomy and physiology between the adult and paediatric population. The understanding of GORD has evolved, with a greater onus on the scope of disease including extraoesophageal disease and treatment pathways (Khoma et al., 2020). This is beyond the capabilities of historic techniques.

The original papers that described these methods often acquired dynamic studies for 1 hr and were bedevilled by movement artefacts that precluded accurate and reproducible ROI analysis and quantitation (Caglar et al., 2003).

Table 1 outlines the different techniques used under the label "Site B." Ten of the 17 utilized a gastroesophageal reflux methodology and the remaining 7 applied a combined oesophageal transit time/gastroesophageal reflux method. "Site A" uses a dedicated gastroesophageal reflux methodology only. The rationale for this decision is that techniques such as barium swallow and manometry provide better spatial resolution and functionality, respectively, for the assessment of swallowing abnormalities and oesophageal transit times.

Fundamental difference between Site A and Site B includes the volume, dose and type of liquid utilized and adherence to a single coherent protocol. The optimal volume of liquid for the adult population is considered 150–200 ml (Caglar et al., 2003) as this simulates a standard adult stomach volume, without overfilling the stomach and inducing reflux (Kjellen et al., 1991). Isotope doses were highly variable among the studies listed in Site B. This is similar to the historic techniques listed in the literature review in Table 2. There is also significant variation in the type of liquid administered, including the acidic and caloric content (especially milk). The use of milk dates back to the genesis of reflux scintigraphy in the paediatric population and integration into the normal feeding cycle. Few studies under "Site B" attempted to assess gastric emptying. Gastric emptying has been found to have an influence on the degree of reflux. This is important in determining the optimal management strategy (Pellegrini, 2001). One centre that did attempt numeric quantitation fitted a linear curve to the data rather than the accepted exponential fit (Ziessman et al., 2009).

The technique implemented at Site A has been validated against the standardized current diagnostic tests for GORD (Burton et al., 2018, 2020; Falk et al., 2015). Findings in 25 normal volunteers have demonstrated that 32% have asymptomatic upright reflux which does not reach the pharynx/laryngopharynx. None of the normal volunteers showed evidence of supine reflux, consistent with the findings in 24-hr oesophageal impedance/pH impedance in normal volunteers (Shay et al., 2004). In this study, 34% of asymptomatic normal volunteers demonstrated evidence of upright reflux and none had supine reflux. This is in line with previous work which came to the conclusion that any supine gastroesophageal reflux is pathological.(Demeester et al., 1976).

Radiopharmaceutical selection is important to the integrity of the test. ^{99m} Tc colloid/phytate is the ideal radiopharmaceutical given its stability and lack of systemic absorption from the gut.

TABLE 1 Individual patient—methodologies under Site B, Diagnosis at Sites A and B, and finding of gastroesophageal reference tests

	Site B Isotope	Site B Dose (MBq)	Site B Liquid used	Site B Volume (ml)	Site B Patient position	Site B Technique
1	Unknown	Unknown	Orange Juice	Unknown	Upright, supine & standing	GER
2	Unknown	Unknown	Milk	200	Upright, supine, prone, right & left lateral	GER
3	(i)^{99m}Tc DTPA;(ii) ^{99m}Tc colloid	(i)40; (ii)40	Unknown	Unknown	Upright, supine	GER
4	^{99m}Tc DTPA	Unknown	Unknown	Unknown	Upright, supine	GER
5	^{99m}Tc DTPA	52	Unknown	Unknown	Upright, supine	GER
6	(i)^{99m}Tc DTPA;(ii) ^{99m}Tc colloid	(i)46; (ii)44	Unknown	Unknown	Upright, supine	GER
7	^{99m}Tc DTPA	Unknown	Water	300	Upright, supine	GER
8	^{99m}Tc Colloid	Unknown	Unknown	120	Upright, semi-supine	GER
9	^{99m}Tc DTPA	Unknown	Unknown	Unknown	Upright, supine	GER
10	Unknown	Unknown	Unknown	Unknown	Upright, supine	GER
11	^{99m}Tc Colloid	50	Water	Unknown	Upright, supine	OTT& GER
12	^{99m}Tc Colloid	Unknown	Milk	Unknown	Upright, supine	OTT& GER
13	^{99m}Tc Colloid	Unknown	Milk	100	Upright & semi-recumbent	OTT& GER
14	(i)^{99m}Tc DTPA;(ii) ^{99m}Tc colloid	(i)44; (ii)40	Unknown	Unknown	Upright, supine	OTT& GER
15	^{99m}Tc DTPA	Unknown	Unknown	Unknown	Upright, supine	OTT& GER
16	Unknown	Unknown	Unknown	Unknown	Upright, supine	OTT& GER
17	(i)^{99m}Tc DTPA;(ii) ^{99m}Tc colloid	(i)40; (ii)40	Unknown	Unknown	Upright, supine	OTT& GER

Abbreviations: ^{99m}Tc, ^{99m} technetium; AbN, abnormal; DTPA, diethylenetriaminepentaacetic acid; GER, gastroesophageal reflux; N, normal; OTT, oesophageal transit time.

This property enables assessment of oesophageal reflux, gastric emptying and pulmonary aspiration with little interference from blood pool or extra-vascular interference, particularly in the lungs. ^{99m}Tc diethylenetriaminepentaacetic acid (DTPA) has been used in several historical techniques although it is absorbed from the gut and has a high volume of distribution in the extra-vascular space (Banerjee et al., 2001). The high background distribution in the lungs impairs detection of pulmonary aspiration (Figures 5 and 6). Experimental work has shown that in the absence of significant background activity, as little as 0.1 MBq of activity in the lungs can be detected by the gamma camera (Ruth et al., 1993), thereby heightening the sensitivity for detecting aspiration of refluxate into the lungs.

Sampling time is an important technical issue in acquisition of reflux studies. Numerous studies have been undertaken to determine the optimal framing rate for the dynamic study of the oesophagus. This has been reported as optimal at 15–30 s (Caglar et al., 2003). Longer framing of ~ 60 s has been shown to miss reflux events (Caglar et al., 2003).

Quantitation is intrinsic to the test as subtle reflux events may be beyond the capabilities of visual detection. Reflux of as little as 1% of stomach activity can be detected in the oesophagus (Caglar

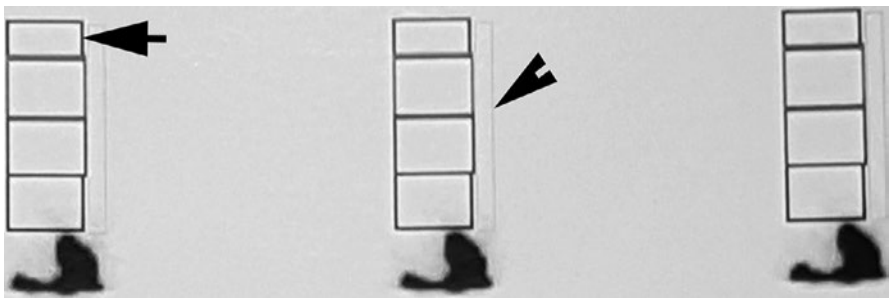


FIGURE 3 Supine dynamic study Site B. The dynamic study shows several frames from a supine acquisition. Four regions of interest over the oesophagus and oropharynx are apparent together with a background region of interest. The intensity of the dynamic study has been thresholded to activity in the stomach, precluding visual analysis for any evidence of reflux in the oesophagus. Also note that the background region (single vertical box) may well overlie the cardiac blood pool activity, leading to erroneous signals if the tracer breaks down, which may influence the curve analysis. Placement of the region of interest for the background over the right lung is a better estimate of background activity

Site B Quantitative analysis	Site B N or AbN	Site A N or AbN	Manometry N or AbN	24-hr pH/impedance N or AbN	Ba Swallow N or AbN	Gastroscopy N or AbN	Peptest N or AbN
No	AbN	AbN	None	Unable to tolerate	AbN	N	None
No	N	AbN	None	AbN	None	None	AbN
No	N	AbN	None	None	None	AbN	None
No	N	AbN	AbN	AbN	None	None	None
No	N	AbN	None	None	AbN	None	None
No	AbN	AbN	AbN	AbN	None	None	None
No	AbN	AbN	AbN	AbN	None	None	None
ROI & Time–activity curves	AbN	AbN	AbN	N	None	AbN	None
No	N	AbN	AbN	Unable to tolerate	Unable to tolerate	None	None
No	N	AbN	None	None	N	None	None
No	N	AbN	N	N	None	AbN	None
No	AbN	AbN	AbN	N	None	AbN	None
Oesophageal Transit time & gastric emptying	AbN	AbN	AbN	AbN	None	None	None
No	N	AbN	N	None	None	AbN	None
Time–activity curves	N	AbN	AbN	AbN	None	None	None
Semi-quantitation	N	AbN	AbN	Unable to tolerate	None	None	None
No	N	AbN	AbN	AbN	None	None	None

et al., 2003). The application of standardized ROI analysis of the oesophagus with appropriate background subtraction (Figure 2) allows derivation of indices such as amplitude, frequency of reflux to the target pharynx/laryngopharynx and clearance of refluxate from the oesophagus (AUC analysis). These are firm numbers that do not require equivocation in decision-making, unlike visual analysis (Caglar et al., 2003). A similar quantitative approach takes the guess-work out of interpreting the delayed study for aspiration into the lungs (Figure 5) (Falk et al., 2015). SPECT/CT shows refluxate in the head and neck structures (Figure 7) and lungs in a binary fashion as there should be no activity at these sites normally without significant pathology.

The Site A technique demonstrates good sensitivity for the detection of gastroesophageal reflux in agreement with other diagnostic gastroesophageal reflux testing. Furthermore, it expands the scope of testing to directly visualize refluxate contaminating extraoesophageal structures such as the laryngopharynx (Figure 7) and lungs which is beyond the scope of the extant testing regimens. These capabilities have been achieved by the advent of hybrid imaging in scintigraphy. The dominant management and treatment approach for the last 30 years have been widespread use of proton-pump inhibitors (PPIs) to control acid reflux, which is effective in 75% of patients with heartburn and regurgitation (Richter, 2014; Vaezi, 2004). Despite this, there is an increasing shift away from long-term use of PPIs due to adverse effects (Yadlapati & Kahrilas, 2018). Furthermore, a significant proportion (up to 40%) of individuals will present with atypical/extraoesophageal symptoms only (Ford, 2005). These symptoms

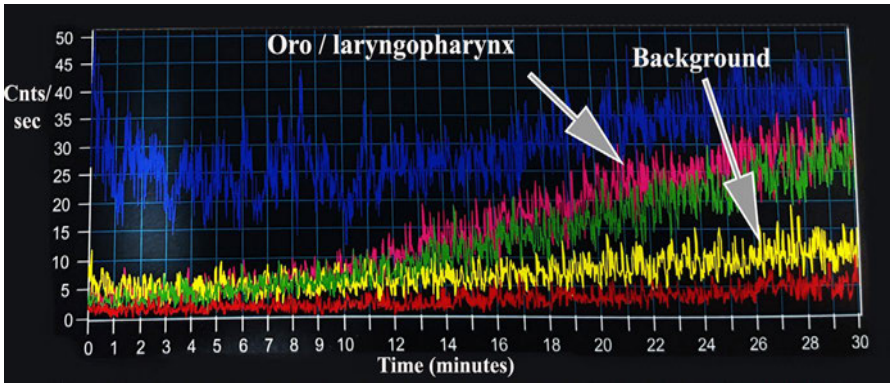


FIGURE 4 Time–activity curve analysis Site B. This study is obtained from the same patient who is illustrated in Figures 1–3. The analysis shows a similar pattern of a rising time–activity curve for the pharynx and upper oesophagus. Note the rising background time–activity curve (yellow) which demonstrates a rising pattern, possibly reflecting cardiac blood pool activity following tracer breakdown (See comment in Figure 3)

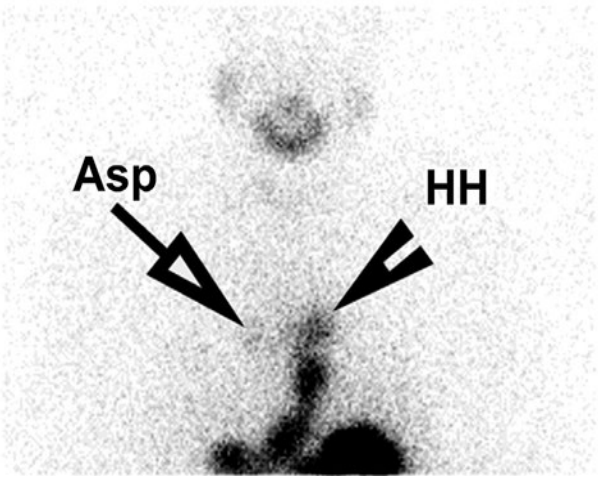


FIGURE 5 Delayed study from the same patient in Figures 1–4 (Site A). The delayed study demonstrates evidence of a hiatus hernia (HH) and aspiration into the central airways (Asp). Note the absence of significant background activity

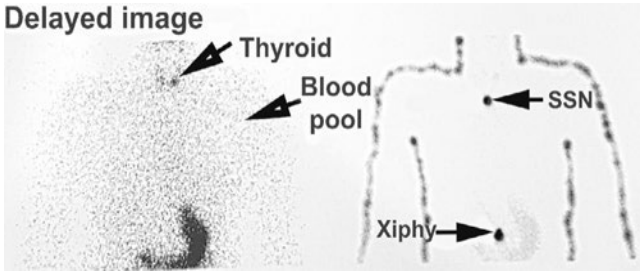


FIGURE 6 Delayed study from the same patient in Figures 1–5 (Site B). Note the degree of blood pool activity and the resultant increase in background which fundamentally outlines the patient's thorax and arms. There is also significant activity in the thyroid gland indicating tracer breakdown. It is difficult to appreciate the hiatus hernia and to assess subtle aspiration into the major airways

require a different approach in order to understand the physiology and pathophysiology of the disease which may be characterized by non-acid or even alkaline reflux (Lee et al., 2018; Sifrim et al., 2005). Scintigraphy is capable of demonstrating reflux regardless of its pH or the coexistence of mixed liquid and gaseous refluxate which may be problematic with oesophageal impedance monitoring (Zerbib & Stoll, 2010).

One weakness of this comparison is the choice of the extant reference testing. The only direct methods are gastroscopy and barium swallows. Gastroscopy visualizes oesophagitis due to exposure of the lower oesophagus to stomach acid, which unfortunately occurs in only 30% of cases with known GORD (Shay et al., 1992). The other technique that offers this is the barium swallow which is even less sensitive and without provocative manoeuvres has a sensitivity of 26%, which rises to 70% with provocation such as the valsalva manoeuvre (Thompson et al., 1994). Other techniques are indirect measures of acidity or impedance. The population in this study had a significant proportion of patients with symptoms of LPR with a mean RSI of 24.7 and a median of 25.9 with only 1 patient having an RSI in the low range (<13). This would push this population into a high pretest probability of reflux disease. Of the two patients not shown to have reflux by the standard reference testing but who tested positive in the Site A scintigraphic reflux testing, both had LPR and 1 showed lung aspiration of refluxate. It is the one major blind spot in the current suite of accepted oesophageal pH/impedance testing (Zerbib et al., 2013; Zerbib & Stoll, 2010).

5 | CONCLUSION

The new scintigraphic reflux technique adds value in the diagnosis, management and treatment of GORD. The technique incorporates

TABLE 2 Literature review of historic scintigraphic techniques

Author	Target	Dose MBq	Liquid	Acquisition view	Quantitation
Piepz et al.	Paediatric	7.4	Milk	Posterior	Freq/Reflux Index
Heyman et al.		7.4–37.0	Milk	Posterior	Time/Act oes/stomach
Seymour et al.		37.0	Milk	Posterior	Time/Act oes/stomach
Orenstein et al.		5.5–11.1	Apple juice	Posterior	Episodes reflux
Caglar et al.		10.0	Milk	Anterior	Grade frequency reflux
Zvi Bar-Sever et al..		9.25	Milk	Posterior	Qualitative
Maurer et al.	Adult	11.1	Orange juice	Posterior	Reflux index
Kazem et al.		18.5	Tea/Water	Anterior	Histogram oesophagus
Fisher et al.		3.7	Saline/HCl	Anterior	Reflux index
Tatsch et al.		10.0	Water	Posterior	ROI oesophagus/Transit times
Bestetti et al.		185	Orange juice	Anterior	ROI/Transit times for oesophagus/stomach
EANM	Mixed	18–185	Milk, Orange juice, Water	Anterior	ROI stomach/Oesophagus
SNM				Anterior or Posterior	Freq and extent of reflux

Abbreviations: Freq, frequency; HCl, hydrochloric acid; Oes, oesophagus; ROI, region of interest.

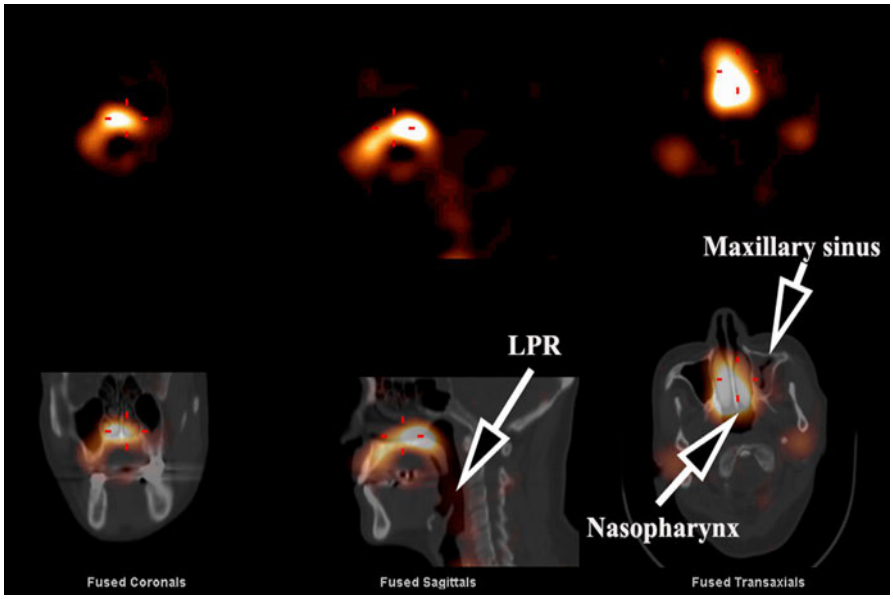


FIGURE 7 SPECT/CT of head and neck. The tomographic study of the head and neck with fusion of the corresponding CT projections demonstrates evidence of refluxate contaminating the laryngopharynx (LPR), nasopharynx and the left maxillary sinus which is opacified by soft tissue thickening

the advances which have been made in the understanding of gastroesophageal and extraoesophageal reflux disease in conjunction with the advent of hybrid technology in scintigraphy. The methodology is pivotal to the integrity, accuracy and reproducibility of this test. This disease is complex in its physiology and pathophysiology. Standardization and attention to detail are crucial to the success of the scintigraphic techniques.

CONFLICT OF INTEREST

There are no conflicts of interests to declare.

ORCID

Leticia Burton https://orcid.org/0000-0001-7234-1267

REFERENCES

Banerjee, S., Ambikalmajan Pillai, M. R., & Ramamoorthy, N. (2001). Evolution of Tc-99m in diagnostic radiopharmaceuticals. *Seminars in Nuclear Medicine*, *31*, 260–277. https://doi.org/10.1053/snuc.2001.26205

Burton, L., Falk, G., Baumgart, K., Beattie, J., Simpson, S., & Van der Wall, H. (2020). Oesophageal clearance in laryngopharyngeal reflux disease: Correlation of reflux scintigraphy and 24-hour impedance pH in a cohort of refractory symptomatic patients. *Molecular Imaging and Radionuclide Therapy*, *29*, 7–16. https://doi.org/10.4274/mirt.galenos.2019.30085

Burton, L., Falk, G. L., Parsons, S., Cusi, M., & Van Der Wall, H. (2018). Benchmarking of a simple scintigraphic test for gastro-oesophageal reflux disease that assesses oesophageal disease and its pulmonary complications. *Molecular Imaging and Radionuclide Therapy*, *27*, 113–120. https://doi.org/10.4274/mirt.10438

Caglar, M., Volkan, B., & Alpar, R. (2003). Reliability of radionuclide gastroesophageal reflux studies using visual and time-activity curve analysis: Inter-observer and intra-observer variation and description of minimum detectable reflux. *Nuclear Medicine Communications*, *24*, 421–428. https://doi.org/10.1097/00006231-200304000-00012

Camilleri, M. (2015) Gastric motility and gastric emptying. In D.K. Podolsky, M. Camilleri, J. G. Fitz, A. N. Kalloo, F. Shanahan, & T. C. Wang (Eds.), *Yamada' s textbook of gastroenterology* (1st ed., pp. 348–366). John Wiley & Sons Ltd.

Cohen, J. (1960). A coefficient of agreement for nominal scales. *Educational and Psychological Measurement*, *20*, 37–46. https://doi.org/10.1177/001316446002000104

Demeester, T. R., Johnson, L. F., Joseph, G. J., Toscano, M. S., Hall, A. W., & Skinner, D. B. (1976). Patterns of gastroesophageal reflux in health and disease. *Annals of Surgery*, *184*, 459–470. https://doi.org/10.1097/00000658-197610000-00009

Elgazzar, A. H. (2011). *A concise guide to nuclear medicine*. Springer-Verlag.

Falk, G. L., Beattie, J., Ing, A., Falk, S. E., Magee, M., Burton, L., & Van der Wall, H. (2015). Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: A definitive diagnostic test? *World Journal of Gastroenterology*, *21*, 3619–3627. https://doi.org/10.3748/wjg.v21.i12.3619

Ford, C. N. (2005). Evaluation and management of laryngopharyngeal reflux. *JAMA*, *294*, 1534–1540. https://doi.org/10.1001/jama.294.12.1534

Khoma, O,, Burton, L., Falk, M. G., Van derWall, H., & Falk, G. L. (2020). Predictors of reflux aspiration and laryngo-pharyngeal reflux. *Esophagus*, *17*, 355–362.

Kjellen, G., Brudin, L., & Hakansson, H. O. (1991). Is scintigraphy of value in the diagnosis of gastroesophageal reflux disease? *Scandinavian Journal of Gastroenterology*, *26*, 425–430.

Lee, Y. C., Kwon, O. E., Park, J. M., & Eun, Y. G. (2018). Do laryngoscopic findings reflect the characteristics of reflux in patients with laryngopharyngeal reflux? *Clinical Otolaryngology*, *43*, 137–143. https://doi.org/10.1111/coa.12914

Pellegrini, C. A. (2001). Delayed gastric emptying in patients with abnormal gastroesophageal reflux. *Annals of Surgery*, *234*, 147–148. https://doi.org/10.1097/00000658-200108000-00003

Richter, J. E. (2014). Current diagnosis and management of suspected reflux symptoms refractory to proton pump inhibitor therapy. *Gastroenterology & Hepatology*, *10*, 547

Ruth, M., Carlsson, S., Mansson, I., Bengtsson, U., & Sandberg, N. (1993). Scintigraphic detection of gastro-pulmonary aspiration in patients with respiratory disorders. *Clinical Physiology*, *13*, 19–33. https://doi.org/10.1111/j.1475-097X.1993.tb00314.x

Savarino, E., Bredenoord, A. J., Fox, M., Pandolfino, J. E., Roman, S., & Gyawali, C. P. (2018). International Working Group for Disorders of Gastrointestinal M and Function. Advances in the physiological assessment and diagnosis of GERD. *Nature Reviews Gastroenterology & Hepatology*, *15*, 323.

Shay, S. S., Abreu, S. H., & Tsuchida, A. (1992). Scintigraphy in gastroesophageal reflux disease: A comparison to endoscopy, LESp, and

24-h pH score, as well as to simultaneous pH monitoring. *American Journal of Gastroenterology*, *87*, 1094–1101.

Shay, S., Tutuian, R., Sifrim, D., Vela, M., Wise, J., Balaji, N., Zhang, X., Adhami, T., Murray, J., Peters, J., & Castell, D. (2004). Twenty-four hour ambulatory simultaneous impedance and pH monitoring: A multicenter report of normal values from 60 healthy volunteers. *American Journal of Gastroenterology*, *99*, 1037–1043. https://doi.org/10.1111/j.1572-0241.2004.04172.x

Sifrim, D., Dupont, L., Blondeau, K., Zhang, X., Tack, J., & Janssens, J. (2005). Weakly acidic reflux in patients with chronic unexplained cough during 24 hour pressure, pH, and impedance monitoring. *Gut*, *54*, 449–454. https://doi.org/10.1136/gut.2004.055418

Thompson, J. K., Koehler, R. E., & Richter, J. E. (1994). Detection of gastroesophageal reflux: Value of barium studies compared with 24-hr pH monitoring. *American Journal of Roentgenology*, *162*, 621–626. https://doi.org/10.2214/ajr.162.3.8109509

Tutuian, R., Vela, M. F., Balaji, N. S., Wise, J. L., Murray, J. A., Peters, J. H., Shay, S. S., & Castell, D. O. (2003). Esophageal function testing with combined multichannel intraluminal impedance and manometry: Multicenter study in healthy volunteers. *Clinical Gastroenterology and Hepatology*, *1*, 174–182.

Vaezi, M. F. (2004). "Refractory GERD": Acid, nonacid, or not GERD? *American Journal of Gastroenterology*, *99*, 989–990.

Vakil, N., van Zanten, S. V., Kahrilas, P., Dent, J., & Jones, R. (2006) The Montreal definition and classification of gastroesophageal reflux disease: A global evidence-based consensus. *American Journal of Gastroenterology*, *101*, 1900–1920; quiz 1943.

Vallabhajosula, S., Killeen, R. P., & Osborne, J. R. (2010). Altered biodistribution of radiopharmaceuticals: Role of radiochemical/pharmaceutical purity, physiological, and pharmacologic factors. *Seminars in Nuclear Medicine*, *40*, 220–241.

Yadlapati, R., & Kahrilas, P. J. (2018). The "dangers" of chronic proton pump inhibitor use. *The Journal of Allergy and Clinical Immunology*, *141*, 79–81.

Yamasaki, T., Hemond, C., Eisa, M., Ganocy, S., & Fass, R. (2018). The changing epidemiology of gastroesophageal reflux disease: Are patients getting younger? *Journal of Neurogastroenterology and Motility*, *24*, 559–569.

Zerbib, F., Roman, S., Bruley Des Varannes, S., Gourcerol, G., Coffin, B., Ropert, A., & Lepicard, P. (2013). Mion F and Groupe Francais De N-G. Normal values of pharyngeal and esophageal 24-hour pH impedance in individuals on and off therapy and interobserver reproducibility. *Clinical Gastroenterology and Hepatology*, *11*, 366–372.

Zerbib, F., & Stoll, D. (2010). Management of laryngopharyngeal reflux: An unmet medical need. *Neurogastroenterology and Motility*, *22*, 109–112.

Ziessman, H. A., Chander, A., Clarke, J. O., Ramos, A., & Wahl, R. L. (2009). The added diagnostic value of liquid gastric emptying compared with solid emptying alone. *Journal of Nuclear Medicine*, *50*, 726–731.

How to cite this article: Burton L, Joffe D, Mackey DW, Van der Wall H, Falk GL. A transformational change in scintigraphic gastroesophageal reflux studies: A comparison with historic techniques. *Clin Physiol Funct Imaging*. 2020;00:1–10. https://doi.org/10.1111/cpf.12677

Am J Nucl Med Mol Imaging 2020;10(6):XXX-XXX
www.ajnmmi.us /ISSN:2160-8407/ajnmmi0123415

Original Article

Findings from a novel scintigraphic gastroesophageal reflux study in asymptomatic volunteers

Leticia Burton[1], Gregory Leighton Falk[2], John Beattie[3], Daniel Novakovic[4], Scott Simpson[5], Hans Van der Wall[1]

[1]CNI Molecular Imaging & University of Notre Dame, Sydney, Australia; [2]Sydney Heartburn Clinic, Concord Hospital & University of Sydney, Australia; [3]Eastwood, Sydney, Australia; [4]Department of ENT Surgery, Canterbury Hospital, Faculty of Medicine and Health, University of Sydney, Australia; [5]Section of Gastroenterology, Sydney Adventist Hospital, Sydney, Australia

Received September 29, 2020; Accepted October 6, 2020; Epub November 15, 2020; Published November 30, 2020

Abstract: Gastroesophageal reflux disease (GERD) is a common and growing problem in most western countries. It may present with the typical symptoms of heartburn and regurgitation or with the effects of extra-esophageal disease. We have developed and validated a scintigraphic test that evaluates reflux at both sites in patients at high risk of laryngopharyngeal reflux and lung aspiration. We hypothesized that the test may be able to separate physiologic reflux from pathological reflux and examined this possibility in normal asymptomatic volunteers. Asymptomatic volunteers were screened with the Belafsky reflux symptom index (RSI) and entered into the trial if scores were less than 13. ^{99m}Tc Phytate was ingested orally and dynamic studies from the pharynx to the stomach were obtained while upright and supine. A delayed study of the thorax was also obtained for lung aspiration of refluxate. Studies were semi-quantitated graphically as time-activity curves. A total of 25 volunteers were studied (13 M, 12 F) with a mean age of 57.5 yr (Range 40-85 yr). None gave a history of heartburn or regurgitation. Mean RSI was 4.1 (range 0-10). Testing showed upright gastroesophageal reflux to the mid-upper esophagus without pharyngeal contamination in 32%. None of the subjects showed supine reflux or lung aspiration. This result corresponds well with intraluminal impedance/pH monitoring in normal volunteers. The scintigraphic reflux test gives similar results to standard intraluminal impedance/pH studies in normal volunteers. A significant proportion of asymptomatic volunteers demonstrate upright reflux only.

Keywords: GERD, gastroesophageal reflux disease, scintigraphy, normal volunteers, asymptomatic, upright reflux

Introduction

Gastroesophageal reflux disease (GERD) is common [1] with a growing prevalence in Western society [2]. The increasing prevalence has been linked to obesity [3] which in itself is linked to an increased prevalence of diabetes mellitus [4, 5]. This triad of diseases contributes to the overall increase in chronic disease, which has been estimated to reach $US10.059 Trillion by 2022, an annual growth rate of 5.4% [6].

It has been estimated that approximately 45% of the population in most western countries suffers from GERD [7]. GERD is a condition that is characterised by the symptoms of heartburn and regurgitation [8]. However, the extra-esophageal manifestations of GERD are less well understood, particularly laryngopharyngeal reflux (LPR) [9]. The symptoms of LPR include throat clearing, persistent cough, globus pharyngeus, and dysphonia. Unfortunately, the diagnosis of LPR has been quite difficult, with recent work indicating that intraluminal esophageal impedance studies utilising a pharyngeal electrode may help to establish the diagnosis, although the technique remains in question due to interobserver variability [10]. Furthermore, there is a significant overlap of GERD and LPR symptomatology, although many of the symptoms of LPR are often overlooked [11]. There is clearly potential for a simple test that can demonstrate LPR and lung aspiration of refluxate with some degree of certainty.

A relatively simple scintigraphic test for the detection of gastroesophageal reflux disease at

Table 1. LARYNGO-PHARYNGEAL REFLUX SYMTPOM INDEX

Symptom	0	1	2	3	4	5
Hoarseness or a problem with your voice						
Clearing your throat						
Excess throat mucous or postnasal drip						
Difficulty swallowing foods, liquids, or pills						
Coughing after you eat or after lying down						
Breathing difficulties or choking episodes						
Troublesome or annoying cough						
Sensations or something sticking in your throat or a lump in your throat						
Heartburn, chest pain, indigestion, or stomach acid coming up						

Within the last month, how did the following problems affect you? (0= No problem to 5= severe problem).

the level of the esophagus and in the extra-esophageal structures such as the laryngo-pharynx and lungs has been developed and validated [12, 13]. As sulfur colloid is no longer available in Australia, the replacement agent, ^{99m}Tc Phytate is currently in use for gastro-esophageal studies such as reflux and gastric emptying. The current study presents the application of the scintigraphic test to a group of normal (asymptomatic) subjects in order to assess the background rate and pattern of physiological gastroesophageal reflux and any characteristics that distinguish it from pathological reflux.

Materials and methods

Subject demographics

Volunteers (≥ 40 years of age) were screened for symptoms of gastroesophageal reflux disease with questions regarding heartburn, regurgitation and globus etc. The reflux symptom index (RSI) of Belafsky et al. [14] was also administered. Nine symptoms pertaining to reflux are graded from 0 (none) to 5 (most severe) and the sum of these scores is the reflux symptom index. The relevant criteria are shown in **Table 1** [14]. Subjects with an RSI score above 13 were excluded from the study. Other exclusion criteria included pregnancy, history of abdominal surgery, asthma or known lung disease.

Ethical considerations

The study was approved by the institutional ethics committee of the University of Notre Dame, Sydney Campus (Reference number 015149S). In adherence to Human Research Ethics Committee (HREC) guidelines all patients were provided with a Participant Information Sheet which outlined the project, risks involved and intended outcomes of the study. Written consent was obtained from all subjects. The use of ionising radiation requires extra provisions to be imposed. This is outlined in the Code of Practice for the Exposure of Humans to Ionizing Radiation for Research Purposes published by the Australian Radiation Protection Safety Agency. The code imposes restrictions that subjects not be under the age of 40 years, but where practical under the age of 50 years.

The dose estimate was extrapolated from the data published in the Knight et al. paper which calculated the effective dose for non-nutrient liquid gastric emptying studies [15].

In accordance with ethics approval the dose, was calculated by a qualified Radiation Safety Officer, who utilised the International Commission on Radiological Protection (ICRP) guidelines to estimate the effective dose to the patient. In optimising patient exposure, ^{99m}Tc Phytate is considered the ideal agent given its characteristic of not crossing the mucosal barrier of the stomach. The radiation exposure of the ^{99m}Tc Phytate for the administered mean dose of 60 MBq was estimated at 0.97 mSv [15].

Scintigraphy

Subjects were fasted for 6 hours prior to the test. A dose of 60-70 MBq of ^{99m}Tc Phytate was administered in 50 mL of water followed by a further 50 mL of water to clear the oro-pharynx and esophagus. Dynamic images were acquired upright for 2 minutes then supine

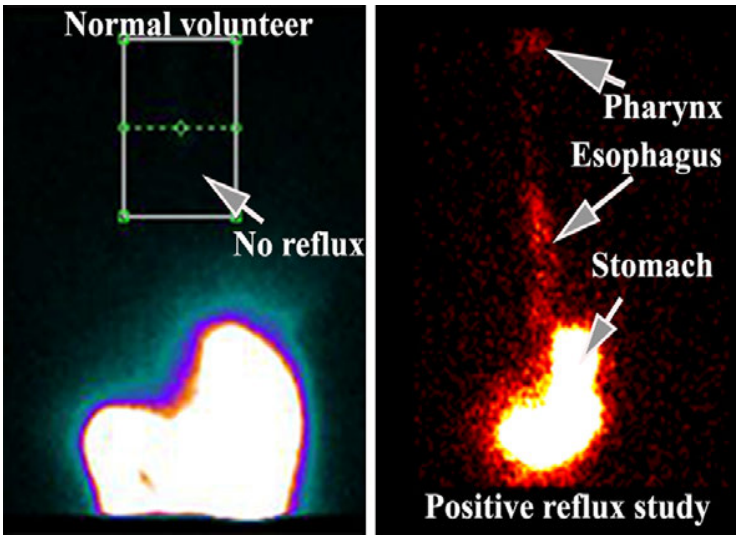


Figure 1. Summed image of frames from a supine study in a normal subject. There is no evidence of significant activity within the esophagus. Compare this with a dynamic study from a patient with symptomatic GERD, where there is significant reflux to the level of the oropharynx and activity visualised within the oesophagus. There is no other activity within the thorax thus identifying that any activity visualised is within the oesophagus and occasionally will be due to immediate aspiration of refluxate into the lungs. The central region of interest is placed just above the penumbra of scatter from the stomach activity. This is the initial step of analysis of the study and is useful for showing subtle reflux.

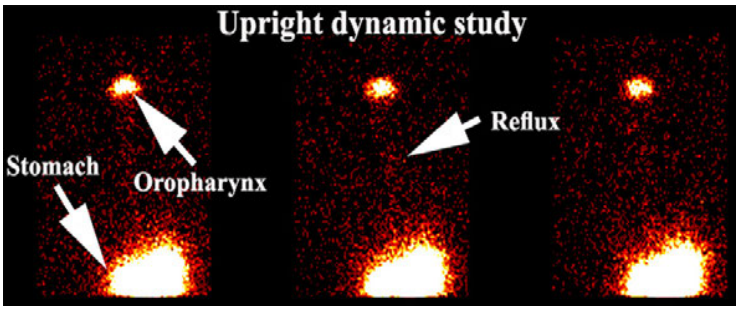


Figure 2. The sequence of dynamic images from the upright study demonstrates subtle reflux to the level of the upper esophagus in a normal volunteer. There is moderate retention of activity in the oropharynx from the initial tracer administration. One of the important technicalities is to place the region of interest below the oropharyngeal activity in order to capture the signal from the laryngopharyngeal region.

for 30 minutes on a Hawkeye 4 hybrid gamma camera (General Electric, Milwaukee, United States) with the mandible and stomach in the field of view (**Figures 1** and **2**). Delayed static imaging was obtained 2 hrs later for assessment of lung aspiration of refluxate. Image analysis is shown in **Figures 3** and **4**. Time-activity curves were obtained for the pharynx/laryngopharynx, upper esophagus and background. Background subtracted curves were obtained for the pharynx/laryngopharynx and upper esophagus. A ratio of the curves for pharynx/laryngopharynx to background was obtained. Liquid gastric emptying was calculated by an exponential fit to the time-activity curve for the stomach. The only structures visualized in the scintigraphic studies are activity in the pharynx/laryngopharynx, esophagus and the stomach. No other organs are visualised until acquisition of the late study which may show activity in the lungs as the scintigraphic agent does not cross the mucosal barrier and there is no significant background activity other than scatter from the stomach.

Statistics

All statistical analysis was obtained with the Statistical Package for the Social Sciences (SPSS) Version 24 (IBM, New York, USA).

Results

Subject demographics

The study group of 25 subjects was comprised of 13 males and 12 females with a mean age of 57.5 years (SD 12.7, Range 40-85 years). None gave a history of heartburn, regurgitation or chronic cough. The mean Belafsky RSI score was 4.1 (Median 4.0, SD 3.6, Range 0-10). Three other subjects were excluded as the scintigraphic scans showed significant GERD when supine and subsequent investigations (pH/impedance and manometry) confirmed disease, although the Belafsky RSI scores were below 13 (silent LPR). These three subjects had findings consistent with LPR on subsequent laryngoscopy.

Scintigraphic scan findings

Eight of 25 subjects (32%) demonstrated gastroesophageal reflux to the mid-upper esophagus when upright which did not reach the pharynx (**Figure 2**). No subject had supine reflux or

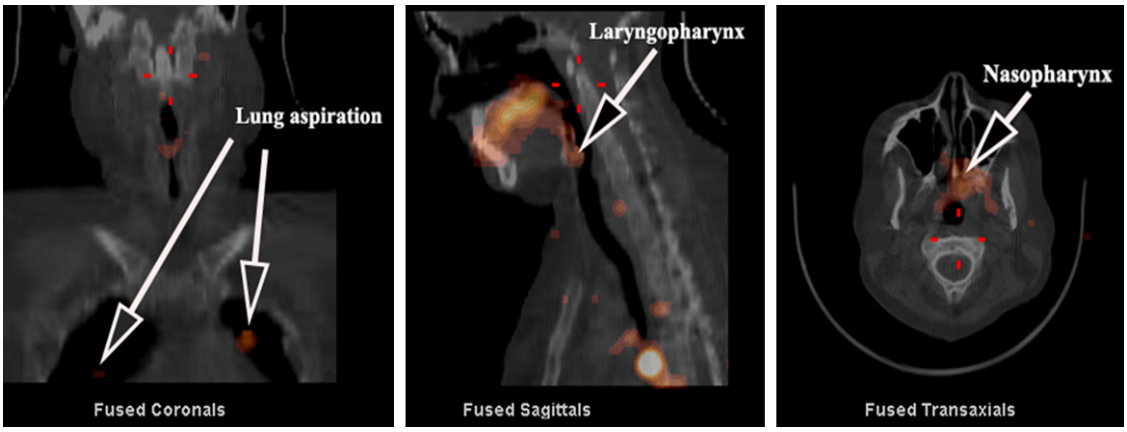


Figure 3. Abnormal patient study. The fused SPECT/CT images of the head, neck and chest demonstrate evidence of refluxate contaminating the oropharynx, laryngopharynx, and nasopharynx. There is also evidence of aspiration of refluxate into the lungs. These studies are routinely acquired in the patient studies. This could not be done with the asymptomatic volunteers due to restrictions of radiation exposure. It provides good orientation of the anatomy when the functional images are fused with the low-dose CT, allowing visualisation of hiatus hernias and possible compression of the cardiac structures.

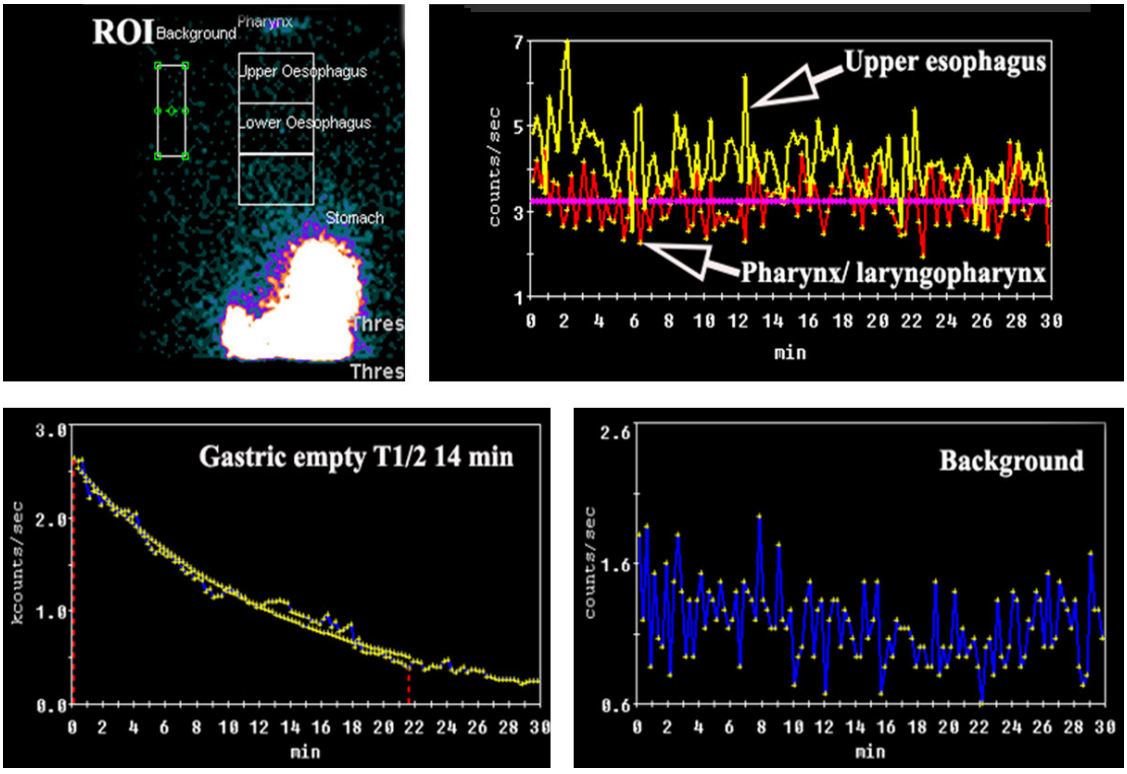


Figure 4. Analysis of supine images. This is a dynamic study obtained for 30 minutes. ROI demonstrates the regions of interest and background over the right lung. The time-activity curves for the pharynx/laryngopharynx (red) with the fitted curve (pink) and the upper esophageal curve (yellow) is shown in the top right panel. Liquid gastric emptying time is shown in the lower left panel. Background activity is illustrated in the lower right panel. Various numeric indices can be derived from these curves.

evidence of aspiration into the lungs in the delayed study.

Analysis of the scintigraphic studies showed no evidence of a rising time-activity curve for the pharynx/laryngopharynx or upper esophagus. Most curves showed a declining pattern with a minority having a flat pattern (n=4). The analysis of the ratio of area under the curve for pharynx/laryngopharynx to background was a me-

an of 1.1 (Median 1.1, SD 0.59, Range 0.10-1.70). The mean amplitude for the pharyngeal/laryngopharyngeal to background curve was 1.2 (Median 1.6, SD 1.1, Range 0-2.3).

There was no significant correlation between subjects with upright gastroesophageal reflux and the RSI ($p>0.05$).

Liquid gastric emptying was a mean of 6.5 minutes (Median: 6.8, SD: 3.4, Range: 1.0-10.0).

The radiation exposure of the ^{99m}Tc Phytate for the administered mean dose of 60 MBq was estimated at 0.97 mSv [15].

Discussion

The findings of upright reflux in 32% of asymptomatic volunteers which does not reach the pharynx is similar to the results of 24-hour ambulatory intraluminal esophageal impedance and pH monitoring in healthy volunteers [16]. In that study, a median of 34% of upright reflux reached the proximal esophagus with acid reflux being twice as common as weakly acidic reflux. This also illustrates the findings previously reported, whereby reproducibility is adversely affected at RSI scores <13, as no patient who demonstrated upright reflux had an abnormal RSI score [17].

The scintigraphic test provides visualisation of reflux in the esophagus in the early dynamic studies and allows an assessment of the maximal level of the reflux episodes (**Figure 2**). With appropriate quantification, one can enumerate these findings (**Figures 3** and **4**). Most importantly, the pH of the refluxate is of no relevance to the degree or extent of reflux as it is a purely functional phenomenon of tracer in water that demonstrates the relevant pathophysiology. Hence the ability of the test to provide visualisation of acidic or basic refluxate, which becomes important in the detection of reflux in patients on maximal antacid therapy or with weakly acidic or alkaline reflux, as often happens in cases of LPR [18].

Physiological upright gastroesophageal reflux is common for a number of reasons. Combined intraluminal esophageal manometry and pH studies in normal volunteers has shown that the lower esophageal sphincter (LES) is more competent when supine than upright [19]. This occurs even when the resting lower esophageal sphincter pressure is normal. The study also showed that physiologic reflux is unaffected by age, is generally asymptomatic and of short duration. It mostly occurs after meals and rarely during sleep. Upright reflux is rapidly cleared by swallowing. The sequence of observations suggests that factors other than gravity influence reflux in the upright position. One could hypothesize that when upright the gastric air bubble moves into the fundus and may induce a venting reflex with a resultant fall in LES pressure. It has been suggested that the air bubble in the fundus may stimulate mechanoreceptors that lead to transient lower esophageal sphincter relaxations, permitting intermittent reflux [20-23]. Demeester et al. [19] did note a much higher incidence of burping in these patients in support of this hypothesis. Comparative manometric measurements between the upright and supine position in normal volunteers has also shown a mean pressure drop of 12 mmHg between the stomach and mid-esophagus when upright [24].

This scintigraphic reflux study is critically dependent on close attention to technical details. The volume of fluid introduced into the stomach is important, as distension by large volumes can induce reflux. Such a phenomenon has been shown to be due to an increase in transient lower esophageal sphincter relaxations as stomach volumes increase from 250 to 500 mL [25]. While smaller volumes may underestimate the degree of reflux, the literature suggests that optimal results are obtained with approximately 150 mL of fluid [26, 27]. Sampling rates for the dynamic studies are also critical. Earlier experience with 60 second sampling found significant degrees of reflux could be missed and more appropriate sampling times have been shown to be in the vicinity of 15 seconds per frame [28]. This does not diminish the ability to detect reflux events as images can be summed together for qualitative assessment (**Figure 1**).

The quantification of the reflux studies has elicited mixed results in the past, with some authors finding it to be helpful [29] and others showing it to be inferior to visual interpretation [30]. We have found it to be helpful as time-activity curves can be utilised to assess the time to clear the esophagus and pharynx/laryngopharynx of refluxate (rising versus declining curves and the ratio of area under the curve for pharynx/laryngopharynx to back-

ground indicating the delay in clearance with rising ratios). One has to be careful with placement of the regions of interest in order to avoid any retained activity in the oropharynx contaminating the data. The top of the region of interest must be placed below the oropharynx in order to include the inferior part of the pharynx and the laryngopharynx (See **Figure 2**). The spikes of increased activity in the time activity curves may be helpful in indicating the frequency of reflux and provide an estimate of the volume of reflux from the amplitude measures (**Figure 4**). These variables have been shown to correlate with intraluminal esophageal impedance/pH studies [31]. Findings in this study showed an amplitude and area under the curve ratio for pharynx/laryngopharynx that was close to 1, indicating it approximated background readings. None of the time-activity curves showed a rising pattern indicative of progressive reflux and/or an impaired clearance mechanism.

The issue of noise, especially related to the small dose of tracer used in the study (~100 MBq) is less of a problem than in other scintigraphic studies as the background level of activity in the thorax is relatively low as there is generally no systemic absorption and the principal contributor is scatter from activity in the stomach. Images can be scatter-corrected to overcome this problem. This is more likely to affect the lower third of the esophagus than the laryngopharyngeal and upper esophageal regions of interest. Poisson noise can be handled by filtering. The consistency of the time-activity curves for the pharyngeal/laryngopharynx and upper esophagus can also distinguish random noise from spikes of activity within the esophagus by the consistency of occurrence in the temporal domain. Modelling has demonstrated that as little as 0.1 MBq can be detected in the lungs, increasing the level of confidence for detection of aspiration of refluxate as there is no significant activity in the lung other than scatter from the stomach [32]. Scatter correction can significantly reduce this activity as well.

Conclusions

This study in normal volunteers has shown that approximately one third of asymptomatic patients have scintigraphically evident gastroesophageal reflux when upright. None of the "normals" demonstrated reflux when supine. No contamination of the pharynx or lungs by refluxate was demonstrated in the normal subjects. Such findings accord well with the large multi-centre trial in normal volunteers utilising intraluminal impedance/pH studies. The scintigraphic study has a low radiation dose, is simple to perform and well tolerated. Although simple, the scintigraphic study requires careful attention to detail in terms of the methodology and technicalities. Appropriate quantification is important in order to maintain fidelity of the technique.

Disclosure of conflict of interest

None.

Address correspondence to: Hans Van der Wall, CNI Molecular Imaging & University of Notre Dame, Suite 101, 5 Bay Drive, Meadowbank, NSW 2114, Sydney, Australia. Tel: +61 2 9736 1040; Fax: +61 2 9736 2095; E-mail: hvanderwall@gmail.com

References

[1] El-Serag HB, Sweet S, Winchester CC and Dent J. Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2014; 63: 871-880.

[2] Yamasaki T, Hemond C, Eisa M, Ganocy S and Fass R. The changing epidemiology of gastroesophageal reflux disease: are patients getting younger? J Neurogastroenterol Motil 2018; 24: 559-569.

[3] El-Serag H. Role of obesity in GORD-related disorders. Gut 2008; 57: 281-284.

[4] Maggio CA and Pi-Sunyer FX. Obesity and type 2 diabetes. Endocrinol Metab Clin North Am 2003; 32: 805-822, viii.

[5] Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS and Marks JS. Prevalence of obesity, diabetes, and obesity-related health risk factors. JAMA 2003; 289: 76-79.

[6] 2019 Global Health Care Outlook. Shaping the future (Press release). United Kingdom: Deloitte Touche Tomatsu, 2019.

[7] Moayyedi P and Axon AT. Review article: gastro-esophageal reflux disease--the extent of the problem. Aliment Pharmacol Ther 2005; 22 Suppl 1: 11-19.

[8] Scott VF. Gastroesophageal reflux disease: diagnosis and management. J Assoc Acad Minor Phys 2000; 11: 12-14.

[9] Ford CN. Evaluation and management of laryngopharyngeal reflux. JAMA 2005; 294: 1534-1540.

[10] Zerbib F and Stoll D. Management of laryngopharyngeal reflux: an unmet medical need. Neurogastroenterol Motil 2010; 22: 109-112.

[11] Drinnan M, Powell J, Nikkar-Esfahani A, Heading RC, Doyle J, Griffin SM, Leslie P, Bradley PT, James P and Wilson JA. Gastroesophageal and extraesophageal reflux symptoms: similarities and differences. Laryngoscope 2015; 125: 424-430.

[12] Falk GL, Beattie J, Ing A, Falk SE, Magee M, Burton L and Van der Wall H. Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? World J Gastroenterol 2015; 21: 3619-3627.

[13] Falk GL and Vivian SJ. Laryngopharyngeal reflux: diagnosis, treatment and latest research. Europ Surg 2016; 48: 74-91.

[14] Belafsky PC, Postma GN and Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice 2002; 16: 274-277.

[15] Knight LC. Update on gastrointestinal radiopharmaceuticals and dosimetry estimates. Semin Nucl Med 2012; 42: 138-144.

[16] Shay S, Tutuian R, Sifrim D, Vela M, Wise J, Balaji N, Zhang X, Adhami T, Murray J, Peters J and Castell D. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: a multicenter report of normal values from 60 healthy volunteers. Am J Gastroenterol 2004; 99: 1037-1043.

[17] Campagnolo AM, Priston J, Thoen RH, Medeiros T and Assuncao AR. Laryngopharyngeal reflux: diagnosis, treatment, and latest research. Int Arch Otorhinolaryngol 2014; 18: 184-191.

[18] Ayazi S, Hagen JA, Zehetner J, Lilley M, Wali P, Augustin F, Oezcelik A, Sohn HJ, Lipham JC, Demeester SR and DeMeester TR. Loss of alkalization in proximal esophagus: a new diagnostic paradigm for patients with laryngopharyngeal reflux. J Gastrointest Surg 2010; 14: 1653-1659.

[19] Demeester TR, Johnson LF, Joseph GJ, Toscano MS, Hall AW and Skinner DB. Patterns of gastroesophageal reflux in health and disease. Ann Surg 1976; 184: 459-470.

[20] Ghisa M, Della Coletta M, Barbuscio I, Marabotto E, Barberio B, Frazzoni M, De Bortoli N, Zentilin P, Tolone S, Ottonello A, Lorenzon G, Savarino V and Savarino E. Updates in the field of non-esophageal gastroesophageal reflux disorder. Expert Rev Gastroenterol Hepatol 2019; 13: 827-838.

[21] Little AF, Cox MR, Martin CJ, Dent J, Franzi SJ and Lavelle R. Influence of posture on transient lower oesophageal sphincter relaxation and gastro-oesophageal reflux in the dog. J Gastroenterol Hepatol 1989; 4: 49-54.

[22] Mittal RK and McCallum RW. Characteristics of transient lower esophageal sphincter relaxation in humans. Am J Physiol 1987; 252: G636-41.

[23] Dent J. Review article: from 1906 to 2006--a century of major evolution of understanding of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2006; 24: 1269-1281.

[24] Johnson LF, Lin YC and Hong SK. Gastroesophageal dynamics during immersion in water to the neck. J Appl Physiol 1975; 38: 449-454.

[25] Holloway RH, Hongo M, Berger K and McCallum RW. Gastric distention: a mechanism for postprandial gastroesophageal reflux. Gastroenterology 1985; 89: 779-784.

[26] Kjellén G, Brudin L and Håkansson H. Is scintigraphy of value in the diagnosis of gastrooesophageal reflux disease? Scand J Gastroenterol 1991; 26: 425-430.

[27] Russell C. Functional evaluation of the esophagus. In: Hill L, editor. The Esophagus Medical and surgical management. Philadelphia: Saunders; 1988. pp. 45.

[28] Seymour JC, West JH and Drane WE. Sequential ten-second acquisitions for detection of gastroesophageal reflux. J Nucl Med 1993; 34: 658-660.

[29] Caglar M, Volkan B and Alpar R. Reliability of radionuclide gastroesophageal reflux studies using visual and time-activity curve analysis: inter-observer and intra-observer variation and description of minimum detectable reflux. Nucl Med Commun 2003; 24: 421-428.

[30] Tuncel M, Kıratlı P, Aksoy T and Bozkurt M. Gastroesophageal reflux scintigraphy: interpretation methods and inter-reader agreement. World J Pediatr 2011; 7: 245-249.

[31] Burton L, Falk GL, Parsons S, Cusi M and Van Der Wall H. Benchmarking of a simple scintigraphic test for gastro-oesophageal reflux disease that assesses oesophageal disease and its pulmonary complications. Mol Imaging Radionucl Ther 2018; 27: 113-120.

[32] Ruth M, Carlsson S, Mansson I, Bengtsson U and Sandberg N. Scintigraphic detection of gastro-pulmonary aspiration in patients with respiratory disorders. Clin Physiol 1993; 13: 19-33.

Original Article
Mol Imaging Radionucl Ther 2020;29:72-78 DOI:10.4274/mirt.galenos.2020.32154

Fungal Pneumonia in The Immunocompetent Host: A Possible Statistical Connection Between Allergic Fungal Sinusitis with Polyposis and Recurrent Pulmonary Infection Detected by Gastroesophageal Reflux Disease Scintigraphy

İmmünokompetan Hastada Fungal Pnömoni: Polipozis ile Alerjik Fungal Sinüzit ve Gastroözefageal Reflü Sintigrafisi ile Saptanan Tekrarlayan Pulmoner Enfeksiyon Arasında Olası İstatistiksel Bağlantı

Leticia Burton[1], Karl Baumgart[2], Daniel Novakovic[3], John Beattie[4], David Joffe[5], Gregory Falk[5], Hans Van der Wall[1]

[1]*University of Notre Dame, CNI Molecular Imaging, Sydney, Australia*
[2]*North Shore Medical Centre, Sydney, Australia*
[3]*University of Sydney, Sydney, Australia*
[4]*Ryde Medical Centre, Sydney, Australia*
[5]*Royal North Shore Hospital, Sydney, Australia*

Abstract

Objectives: Fungal pneumonia in the immune competent host is a rarity with few reported cases in the literature. We present a series of 7 cases of recurrent fungal pneumonia in association with allergic fungal rhinosinusitis and gastroesophageal reflux disease (GERD). We hypothesised that recurrent infection may have been transported from the infected paranasal sinuses into the lung by GERD as the process was terminated by surgical fundoplication in 2 of these patients.

Methods: Patients were recruited into the study if they were immune competent and had recurrent fungal pneumonia and GERD. Allergic fungal rhinosinusitis was proven by biopsy. GERD was investigated by a scintigraphic test that assessed local oesophageal disease, lung aspiration and head and neck involvement with a hybrid gamma camera and X-ray computed tomography.

Results: All patients were shown to have GERD with 5/7 showing paranasal sinus contamination and 7/7 showing laryngopharyngeal involvement and 6/7 lung aspiration. One patient had characteristics strongly predictive of aspiration. Fundoplication led to cessation of fungal lung infection in two patients.

Conclusion: Recurrent fungal pneumonia in the immune competent host should raise the possibility of re-infection from the paranasal sinuses, especially in patients with GERD.

Keywords: Allergic, fungal, rhinosinusitis, pneumonia, reflux, scintigraphy

Öz

Amaç: İmmünokompetan hastada fungal pnömoni literatürde az sayıda olguda bildirilmiştir. Bu yazıda alerjik fungal rinosinüzit ve gastroözofageal reflü hastalığı (GÖRH) ile ilişkili tekrarlayan fungal pnömonisi olan 7 olgu sunulmuştur. Bu hastaların 2'sinde cerrahi fundoplikasyon ile tekrarlayan fungal pnömoni atakları sonlandığı için, tekrarlayan enfeksiyonun enfekte paranazal sinüslerden GÖRH ile akciğere taşındığını varsaydık.

Yöntem: Tekrarlayan fungal pnömonisi ve GÖRH olan immünokompetan hastalar çalışmaya alındı. Alerjik fungal rinosinüzitin varlığı biyopsi ile kanıtlandı. GÖRH, lokal özofagus hastalığı, akciğer aspirasyonu ve baş-boyun tutulumunu bir hibrit gamma kamera ve X-ışını bilgisayarlı tomografi ile değerlendiren bir sintigrafik test ile araştırıldı.

Address for Correspondence: Hans Van Der Wall MD, University of Notre Dame, CNI Molecular Imaging, Sydney, Australia
Phone: +61297361040 **E-mail:** hvanderwall@gmail.com ORCID ID: orcid.org/0000-0003-4184-3330
Received: 10.12.2019 **Accepted:** 03.02.2020

Bulgular: Tüm hastalarda GÖRH olduğu gösterildi. Yedi hastanın 5'inde paranazal sinüs kontaminasyonu, tamamında laringofaringeal tutulum ve 6'sında akciğer aspirasyonu gösterildi. Bir hastada aspirasyonun olduğunu güçlü bir şekilde öngören özellikler vardı. Fundoplikasyon iki hastada fungal akciğer enfeksiyonunun kesilmesine yol açtı.

Sonuç: İmmünokompetan hastalarda tekrarlayan fungal pnömoni, özellikle GÖRH olan hastalarda paranazal sinüslerden re-enfeksiyon olasılığını düşündürmelidir.

Anahtar kelimeler: Alerjik, mantar, rinosinüzit, pnömoni, reflü, sintigrafi

Introduction

The Aspergillus species of fungus is widespread and generally acquired by inhalation of airborne spores. The immunocompetence of the host is a critical factor in the establishment of invasive infection. More rarely, infection may occur in the immunocompetent host, as has been described by a number of authors (1,2,3). Such cases have been described since 1959 (4). These cases include patients with chronic fungal infections of the maxillary sinuses, mediastinum, lymph nodes and direct pulmonary involvement. The cohort in which the biggest of these series has been described (3) have consisted relatively young men and women. In that series 9 of 18 patients had allergic fungal sinusitis with polyposis with a background of chronic rhinosinusitis.

This paper presents 7 patients with recurrent pulmonary infections who are distinguished from most previous reports in terms of a connection between recurrent fungal pneumonia and allergic fungal sinusitis with polyposis. Several of these patients had undergone lobectomy to eradicate the primary infection of the lungs with subsequent recurrence elsewhere in the lungs. All patients gave a history of symptomatic gastroesophageal reflux disease (GERD), and were tested with a scintigraphic reflux study (5,6) to evaluate the presence of disease within the oesophagus, paranasal sinuses and the possibility of aspiration of refluxate into the lungs. The findings led to exploration of a possible connection between these conditions and surgical intervention, supporting the conclusions.

Based on this case series, we hypothesised that there might be a connection between severe GERD with aspiration into the lungs, recurrent pulmonary fungal infections and allergic fungal sinusitis with polyposis

Materials and Methods

Patient Group

Consecutive patients with fungal pneumonia were referred to a single Nuclear Medicine practice as part of a large research study to evaluate extra-oesophageal manifestations of GERD over a period of 3 years. All patients had established GERD on the basis of 24-hour pH, manometry and impedance monitoring and most had undergone upper gastrointestinal endoscopy and ear, nose and throat assessment with laryngoscopy. The presence of allergic fungal sinusitis with polyposis had been confirmed by biopsy of tissue from the paranasal sinuses, although culture had been unsuccessful in 3 of 7 cases. There was no evidence of invasion or mycetoma formation in these patients. Microscopy of lung tissue obtained by lobectomy or bronchoscopy confirmed semi-invasive fungal disease (7 aspergillus species) in all patients. Immunological testing had confirmed immune competence in all patients. Patients with fungal disease being treated for malignancy or following organ transplantation were excluded from the study.

All patients were on proton pump inhibitor (PPI) therapy at the time of the study and were clinically assessed with the Belafsky Reflux symptom index score (7).

Ethical Considerations

A database of patients with either proven or suspected GERD/Laryngopharyngeral reflux (approved by the Institutional Ethics Committee of University of Notre Dame 015149S) was maintained prospectively.

Statistical Analysis

All statistical analysis was performed on the Statistical Package for the Social Sciences (SPPS Version 24, IBM, New York, USA).

Scintigraphic Reflux Study

Patients were fasted for 12 hours and medications ceased for the 24-hours prior to the test. While upright, patients were positioned in front of a Hawkeye 4 gamma camera (General Electric, Milwaukee, USA) with markers on the mandible and stomach to ensure regions of interest were in the field of view of the camera. Patients consumed 50-100 mL of water with 60-100 MBq of Technetium Phytate followed by flushing with 50 mL of water to clear the mouth and oesophagus from radioactivity. Dynamic images of the pharynx, oesophagus and stomach were obtained for 2 minutes at 15 secs per frame into a 64x64 matrix while upright. This was followed by a 30-minute dynamic in the supine position. Delayed images were obtained at 2

hours to assess the presence of aspiration of tracer activity into the lungs. Following acquisition of the planar image of the lungs, a single photon emission computed tomography (SPECT) study of the head, neck and lungs was obtained and registered with X-ray computed tomography (CT) of the region. These images were reconstructed, fused and displayed in standard projections. Dynamic images were analysed by time activity curves over the pharynx/laryngopharynx, upper and lower half of the oesophagus and by a background region over the right side of the chest, away from the stomach and oesophagus. Delayed images were analysed by a line profile over the lungs. Time activity curves were graded as showing no GERD, falling, flat or rising curves. Area under the curve and maximal amplitude compared to background were estimated. Liquid gastric emptying half-time was determined from the 30-minute supine acquisition with a single exponential fit to the data.

Results

Patient data. A total of 7 patients were included in the study with an average age of 62 years (range= 47-74 years). There were 5 females and 2 males. The average length of history of sinusitis was 7 years (range=4-8 years). All had been treated for recurrent biopsy-proven allergic fungal sinusitis with polyposis of the paranasal sinuses and lung infection over a period of approximately 4-5 years. Five of 7 patients were on concurrent therapy for asthma, although lung function testing had shown no reversible component. Three patients had undergone lobectomy of the lungs to eradicate the infection without success. All patients had undergone paranasal sinus surgery with recurrence of infection within weeks of the surgery. Biopsy of tissue from the paranasal sinuses/lungs failed to grow the fungus in media in 3 patients, although microscopy confirmed semi-invasive disease in all 7 patients. Antifungal antibiotics utilised in treatment included erbinafine, fluconazole, itraconazole, voriconazole, posaconazole and griseofulvin.

High resolution CT scanning of the lungs demonstrated pulmonary fibrosis in 3 patients, with bronchiectasis in 2 of these and a further patient with bronchiectasis.

All 7 patients had previously been investigated for GERD with 24-hour pH manometry and impedance that confirmed reflux disease and been commenced on long-term PPI and other therapy (Nexium-5, Somac-3, Losec-1, Ranitidine-4, Tazac-1, Motilium-1). Four patients had no symptoms of heartburn, globus or regurgitation, while 3 gave a history of daily symptoms. The average Belafsky score (7) was 20.0 (range: 0-35.0).

Two of the seven patients who had undergone lobectomy for recurrent fungal pneumonia and shown lung aspiration of refluxate in the scintigraphic studies underwent laparoscopic fundoplication. These patients became disease free in the lungs within 3 months while on antifungal therapy and at follow-up showed reduced parameters of reflux and no further lung aspiration of refluxate.

Scintigraphic findings. All 7 patients showed evidence of significant intermittent or continuous full-column GER (Figure 1) with pharyngeal/ laryngopharyngeal contamination by refluxate. The average amplitude of the refluxate was 4.8 times higher than background and the average frequency of reflux to the larygopharynx in supine position was 22 episodes in 30 minutes (range=10-50 episodes). Liquid gastric emptying was normal in 2 patients (half-clearance time <16.0 minutes) while 5 were abnormal with half-clearance times ranging from 18.0 to 124.0 minutes (mean=56.8 minutes). Sample analysis is shown in Figure 1.

Analysis of the pattern of time-activity curves for the pharynx/laryngopharynx showed 5 rising curves when upright with 2 showing a falling pattern. When supine, 4 showed rising curves and 3 falling curves.

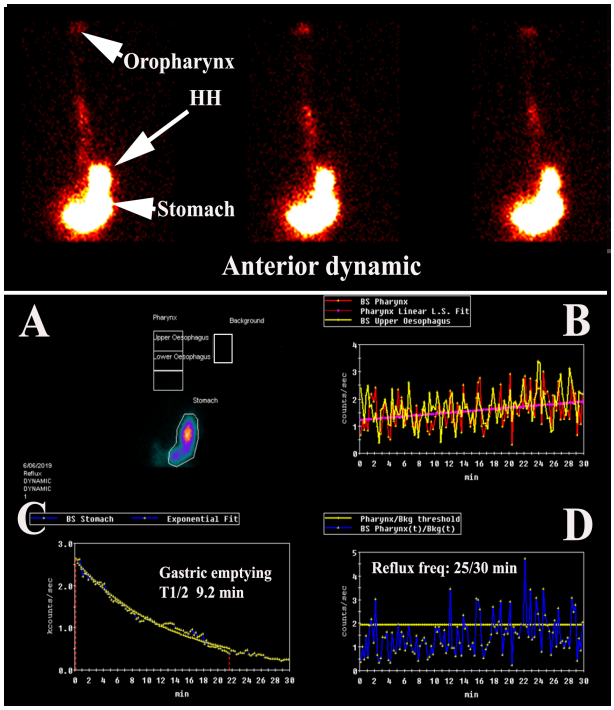


Figure 1. Initial anterior dynamic image with the analysis of the dynamic image in the panel below. Three 15 second frames of the supine dynamic image are shown in the panel above with the oropharynx and stomach labelled. The patient also has a hiatus hernia. The analysis in the panel below shows the regions of interest in A and the time-activity curves for the pharynx/laryngopharynx (red) and osesophagus (yellow) and the curve fitted to the pharynx/laryngopharyngeal curve (pink) in B. Liquid gastric emptying is shown in C with a single exponential curve fitted to the time-activity curve for the stomach. The frequency of reflux to the pharynx/laryngopharynx is shown in D

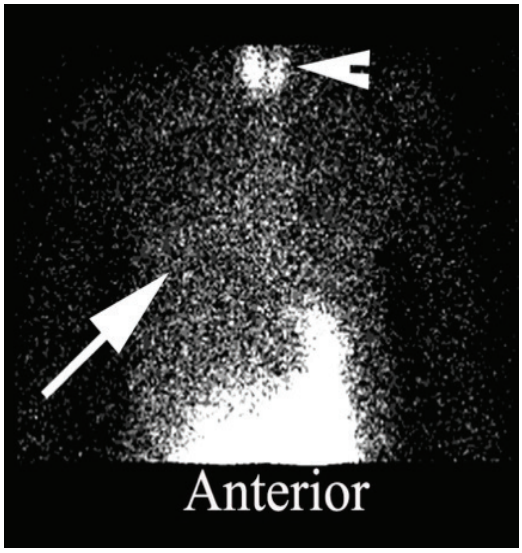


Figure 2. Delayed image of the anterior thorax obtained at two hours demonstrating aspiration of refluxate into predominantly the right lung (arrow). Radiopharmaceutical breakdown in the delayed image sometimes leads to free pertechnetate formation, which is taken up by the thyroid gland and is apparent in this study (arrowhead)

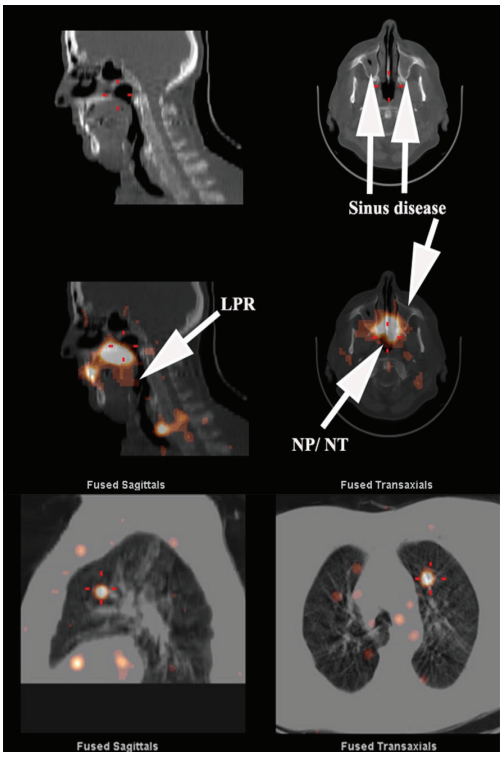


Figure 3. SPECT/CT image of head, neck and lungs. The CT image shows evidence of soft tissue thickening within the maxillary sinuses (arrows) consistent with sinus disease. The fused image in the middle panel demonstrates LPR, NP, NT and maxillary sinus contamination by refluxate. The lower panel shows aspirated refluxate within the lung tissue. Some misregistration is inevitable in the lungs due to respiratory motion and frequent coughing in many of these patients.

SPECT: Single photon emission computed tomography, CT: Computed tomography, LPR: Laryngopharyngeal, NP: Nasopharyngeal, NT: Nasal turbinate

Six of the 7 cases showed evidence of pulmonary aspiration of refluxate in the delayed study (Figure 2) and the patient who did not show had rising time-activity curves for thelaryngopharyngeal region in the upright and supine positions.

SPECT/CT imaging of the head, neck and lungs (Figure 3-5) demonstrated laryngopharyngeal contamination by refluxate in all 7, nasopharyngeal in 6 and maxillary sinus contamination in 5 patients. One patient had right middle ear contamination by refluxate. Lung aspiration of refluxate was confirmed in 6 patients.

Discussion

This series raises a number of troubling issues pertaining to the relationship between rhinosinusitis and GERD. What is the role of GERD in sustaining the inflammatory process in the paranasal sinuses? Is it a primary cause or a promoter or is it a bystander phenomenon? How can one establish whether GERD involves the paranasal sinuses? What is the

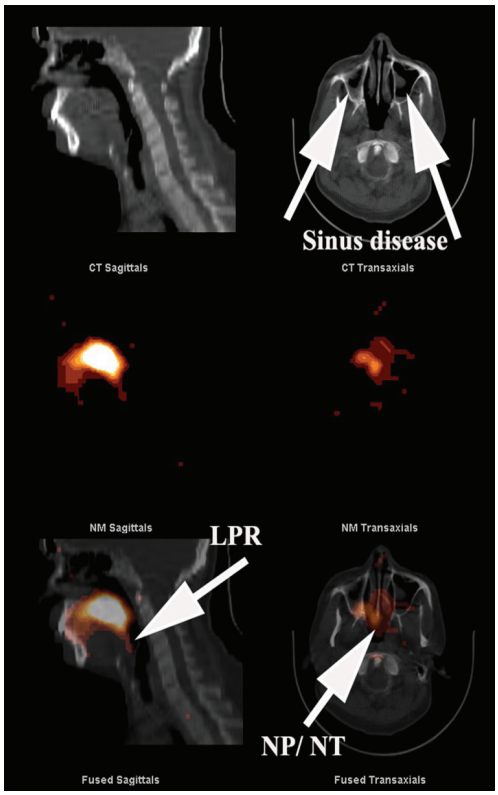


Figure 4. SPECT/CT image of head and neck. The upper panel of CT images with evidence of polyposis of both maxillary sinuses consistent with sinus disease. The fused images in the lower panel demonstrate evidence of LPR as well as contamination of the NP, NT and both maxillary sinuses. The central panel shows the scintigraphic images from the region in the absence of anatomical landmarks

SPECT: Single photon emission computed tomography, CT: Computed tomography, LPR: Laryngopharyngeal, NP: Nasopharyngeal, NT: Nasal turbinate

relationship between chronic fungal sinusitis and recurrent fungal pneumonia? Five of seven patients in this series were diagnosed as having asthma and treated for asthma although lung functions tests showed no reversibility after bronhcodilators. Many of these troubling issues can be explained by the scintigraphic reflux studies as both local disease in the oesophagus and extra-oesophageal structures can be physically visualised and at least semi-quantitated as shown. All 7 patients showed laryngopharyngeal contamination by refluxate with 6 also demonstrating lung aspiration. Laryngopharyngeal reflux was supported by the Belafsky scores of~20.0.

The majority of the patients in this case series gave a good history of established rhinosinusitis (8) predating the episodes of fungal pneumonia. They also had established and treated gastroesophageal reflux. It raises the question of how fungal infection can establish itself in the paranasal

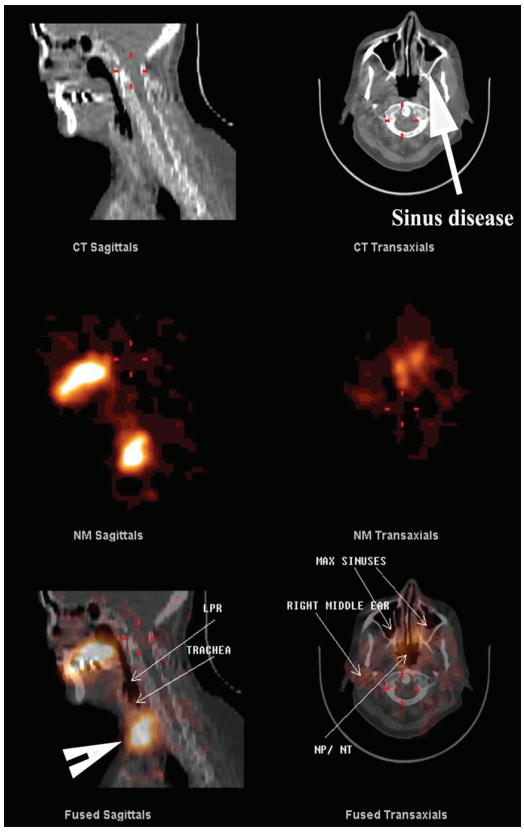


Figure 5. SPECT/CT image of head and neck. The upper panel of CT images demonstrates evidence of sinus disease in the left maxillary sinus. Fused images in the lower panel confirm the presence of refluxate contaminating the LPR, trachea, maxillary sinuses, NP, nasal NT and the right middle ear. The middle panel demonstrates the scintigraphic images and the difficulty in ascribing anatomical sites to these images without the CT study. Note uptake in the thyroid gland (arrowhead) in the fused sagittal image due to breakdown of the radiopharmaceutical in the delayed images

SPECT: Single photon emission computed tomography, CT: Computed tomography, LPR: Laryngopharyngeal, NP: Nasopharyngeal, NT: Nasal turbinate

sinuses in an immune competent host. The combination of pseudostratified ciliated epithelium which is held together by tight junctions and protein secretions that have antimicrobial properties generally protects the host from infection (9). Breakdown of this barrier occurs in response to either allergic or inflammatory stimuli with secretion of epithelial-derived thymic stromal lymphopoietin, which in an up-regulated state may damage tight junctions, together with other toxic molecules such as the interleukins and interferon (9,10). All seven patients in this study had established GERD with the scintigraphic study showing paranasal sinus contamination by refluxate in the majority. There is a body of evidence that shows pepsin in refluxate as an agent capable of damaging nasal epithelium, which may have contributed or potentiated chronic rhinosinusitis (11). The seminal question is whether fungi initiate the inflammatory change or exploit a pre-existing inflammatory condition. The balance of opinion is that fungi initiate the inflammatory changes and then exploit the breakdown in defensive barriers (12). Luong et al. (13) demonstrated that common etiologic fungal antigens induced peripheral blood mononuclear cells to secrete elevated levels of interleukin 4 and 5 in patients with allergic fungal rhinosinusitis compared to normal controls. Inflammatory changes may also be promoted by coexistent staphylococcus aureus infection of the paranasal sinuses with the elevated IgE response to enterotoxin A and B, superantigens which are secreted by the bacterium (14). Pathogenic organisms such as fungi create a favourable environment for growth in the paranasal sinuses and subsequently produce conditions (eg. biofilms) that help evade the host immun system, antibiotic therapy and even surgical intervention (15).

The key finding that supports the hypothesis of recurrent infection of the lungs from established fungal disease of the paranasal sinuses is the response to laparoscopic fundoplication. It clearly implies a fundamental role for GERD with extra-oesophageal manifestations in the paranasal sinuses and subsequent aspiration of refluxate into the lungs. This is a complex issue as virtually all patients were on maintenance PPI therapy for the clinically diagnosed reflux disease. As has been shown, patients on high-dose PPI therapy, will continue to experience non-acid or even alkaline reflux which may be asymptomatic (16). This raises the possibility that PPI therapy in this cohort may have reduced the sterilisation effect of acid reflux on fungal disease in the paranasal sinuses and encouraged growth of the fungus in an alkaline environment. The change in pH of growth medium has been shown to induce fungal gene expression involved in the regulation of extracellular enzymes that may promote growth (17). While Aspergillus species are capable of growth across the entire range of pH

from 2 to 11, they have been shown to be more tolerant to alkaline pH for growth (18). Furthermore, the alkaline pH with co-existent gastric mucositis may have reduced the absorption of many of the anti-fungal antibiotics utilised in these patients, with the exception of fluconazole (19).

GERD could play the role of transporter, particularly in its extra-oesophageal reach through the paranasal sinuses, laryngopharynx and airways as happened in all 7 patients. This system would need to be operational for a significant period, particularly when the patient was supine and the protective mechanisms against reflux were minimised, most likely during sleep (20,21). The possibility of assessing extra-oesophageal manifestations of GERD has until recently been a matter of deductive reasoning or based on observation of inflammatory change in the laryngopharynx on laryngoscopy (22). More recently, 24-hour impedance/pH monitoring has shown some promise although reproducibility has been an issue (23). The scintigraphic reflux technique utilised in the current study allows direct visualisation of refluxate within the sinuses, laryngopharynx and lungs (Figure 3, 4, 5) in addition to demonstrating disease within the oesophagus. Entry of refluxate into the paranasal sinuses was evident in 5 of 7 patients and aspiration into the lungs in 6 of 7 with recurrent fungal pneumonia. The scintigraphic reflux study assesses patients for lung aspiration after a sampling period of 2 hours, during which the patient is supine for only 30 minutes. Previous work has shown that rising time activity curves for the pharynx/laryngopharynx and upper oesophagus have a positive predictive value of 90% for lung aspiration of refluxate (5). The only patient who did not show aspiration in the 2-hour study had this pattern of activity for the laryngopharynx and upper oesophagus. It does suggest a high likelihood of aspiration during prolonged recumbency, especially during sleep (20,21).

The inability to eradicate fungal disease from the lungs has suggested more complex pathology, as even pulmonary lobectomy of the infected sites has not solved the problem. There has appeared to be a source of recurrent fungal infection, raising the strong possibility that the disease in the paranasal sinuses may have been the source, and the passage of refluxate through the sinuses, the main transport mechanism for infected tissue into the lungs. The only method of breaking the cycle of infection and re-infection has appeared to be to disrupt recurrent gastro-oesophageal reflux with surgical fundoplication. This technique effectively reduces the volume of reflux and interrupts what has appeared to be a recurrent transport system from the sinuses into the lungs in this particular group of patients.

Diagnosis of aspergillosis within the paranasal sinuses has proven to be problematic as engendering fungal growth in external media has sometimes been unproductive. However, microscopy of biopsies from the sinuses with silver staining or molecular techniques has demonstrated semi-invasive disease of the mucosa with a diagnosis of allergic fungal sinusitis with polyposis. This is important, as studies of normal (uninfected) paranasal sinuses has shown a biome in which fungal elements may be inhaled as airborne contaminants and trapped in the paranasal mucous, being shuttled to the oropharynx for removal (24). One of the significant problems with molecular techniques is the detection of molecular material of inactive microorganisms (24). The inability to culture fungi from biopsy material may be related to the formation of biofilms, which inhibits growth in culture media, as has been shown in a number of reviewed studies (24). The type of biofilm (eg. haemophilus influenza versus staphylococcus aureus) may affect the severity of disease by protecting pathogenic organisms from the effects of antibiotics in chronic rhinosinusitis and even affect the success of surgery (15,25,26).

Conclusion

Fungal pneumonia in the immunocompetent host is rare. It may well begin in the paranasal sinuses, as has been shown in one of the larger series and when coupled with the appropriate pre-conditions become chronic and increase the risk of spread to the lungs. This series offers a good case to support the hypothesis that recurrent fungal pneumonia may be due to re-infection of the lungs from allergic fungal sinusitis with polyposis by passage of GER through the paranasal sinuses and into the lungs.

Ethics

Ethics Committee Approval: Institutional Ethics Committee of University of Notre Dame 015149S.

Informed Consent: Consent forms were filled out by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.V.W., G.F., Concept: L.B., J.B., Design: L.B., D.J., Data Collection or Processing: H.V.W., K.B., L.B., D.N., Analysis or Interpretation: H.V.W., Literature Search: L.B., G.F., Writing: L.B., H.V.W., D.N., G.F.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: No financial issues to declare as no funding was received for the study.

References

1. Hillerdal G, Benson L, Lindgren A, Hjertquist SO. Disseminated pulmonary aspergillosis in a previously healthy young woman. Scand J Infect Dis 1984;6:217-222.
2. Karam GH, Griffin FM Jr. Invasive pulmonary aspergillosis in nonimmunocompromised, nonneutropenic hosts. Rev Infect Dis 1986;8:357-363.
3. Karim M, Alam M, Shah AA, Ahmed R, Sheikh H. Chronic invasive aspergillosis in apparently immunocompetent hosts. Clin Infect Dis 1997;24:723-733.
4. Finegold S, Will D, Murray F. Aspergillosis, a review and report of twelve cases. Am J Med 1959;27:463-482.
5. Falk GL, Beattie J, Ing A, Falk SE, Magee M, Burton L, Van der Wall H. Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? World J Gastroenterol 2015;21:3619-3627.
6. Falk M, Van der Wall H, Falk GL. Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms. Nucl Med Commun 2015;36:625-630.
7. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice 2002;16:274-277.
8. Bent JP 3rd, Kuhn FA. Diagnosis of allergic fungal sinusitis. Otolaryngol Head Neck Surg 1994;111:580-588.
9. Patel NN, Kohanski MA, Maina IW, Workman AD, Herbert DR, Cohen NA. Sentinels at the wall: epithelial-derived cytokines serve as triggers of upper airway type 2 inflammation. Int Forum Allergy Rhinol 2019;9:93-99.
10. Lavigne P, Lee SE. Immunomodulators in chronic rhinosinusitis. World J Otorhinolaryngol Head Neck Surg 2018;4:186-192.
11. Southwood JE, Hoekzema CR, Samuels TL, Wells C, Poetker DM, Johnston N, Loehrl TA. The Impact of Pepsin on Human Nasal Epithelial Cells In Vitro: A Potential Mechanism for Extraesophageal Reflux Induced Chronic Rhinosinusitis. Ann Otol Rhinol Laryngol 2015;124:957-964.
12. Plonk DP, Luong A. Current understanding of allergic fungal rhinosinusitis and treatment implications. Curr Opin Otolaryngol Head Neck Surg 2014;22:221-226.
13. Luong A, Davis LS, Marple BF. Peripheral blood mononuclear cells from allergic fungal rhinosinusitis adults express a Th2 cytokine response to fungal antigens. Am J Rhinol Allergy 2009;23:281-287.
14. Dutre T, Al Dousary S, Zhang N, Bachert C. Allergic fungal rhinosinusitis-more than a fungal disease? J Allergy Clin Immunol 2013;132:487-489.
15. Foreman A, Wormald PJ. Different biofilms, different disease? A clinical outcomes study. Laryngoscope 2010;120:1701-1706.
16. Mainie I, Tutuian R, Shay S, Vela M, Zhang X, Sifrim D, Castell DO. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. Gut 2006;55:1398-1402.
17. Caddick MX, Brownlee AG, Arst HN Jr. Regulation of gene expression by pH of the growth medium in Aspergillus nidulans. Mol Gen Genet 1986;203:346-353.
18. Wheeler KA, Hurdman BF, Pitt JI. Influence of pH on the growth of some toxigenic species of Aspergillus, Penicillium and Fusarium. Int J Food Microbiol 1991;12:141-149.
19. Brüggemann RJ, Alffenaar JW, Blijlevens NM, Billaud EM, Kosterink JG, Verweij PE, Burger DM. Clinical Relevance of the Pharmacokinetic Interactions of Azole Antifungal Drugs with Other Coadministered Agents Clin Infect Dis 2009;48:1441-1458.
20. Lee KK, Birring SS. Cough and sleep. Lung 2010;188(Suppl 1):91-94.
21. Orr WC. Sleep and gastroesophageal reflux: what are the risks? Am J Med 2003;15(Suppl 3):109-113.
22. Habermann W, Schmid C, Neumann K, Devaney T, Hammer HF. Reflux symptom index and reflux finding score in otolaryngologic practice. J Voice 2012;26:123-127.
23. Zerbib F, Roman S, Bruley Des Varannes S, Gourcerol G, Coffin B, Ropert A, Lepicard P, Mion F; Groupe Français De Neuro-Gastroentérologie. Normal values of pharyngeal and esophageal 24-hour ph impedance in individuals on and off therapy and interobserver reproducibility. Clin Gastroenterol Hepatol 2013;11:366-372.
24. Boase S, Foreman A, Cleland E, Tan L, Melton-Kreft R, Pant H, Hu FZ, Ehrlich GD, Wormald PJ. The microbiome of chronic rhinosinusitis: culture, molecular diagnostics and biofilm detection. BMC Infect Dis 2013;13:210.
25. Singhal D, Psaltis AJ, Foreman A, Wormald PJ. The impact of biofilms on outcomes after endoscopic sinus surgery. Am J Rhinol Allergy 2010;24:169-174.
26. Foreman A, Psaltis AJ, Tan LW, Wormald PJ. Characterization of bacterial and fungal biofilms in chronic rhinosinusitis. Allergy Rhinol (Providence) 2010;1:10.

Original Article
Mol Imaging Radionucl Ther 2020;29:7-16 DOI:10.4274/mirt.galenos.2019.30085

Esophageal Clearance in Laryngopharyngeal Reflux Disease: Correlation of Reflux Scintigraphy and 24-Hour Impedance/Ph in a Cohort of Refractory Symptomatic Patients

Laringofarengeal Reflü Hastalığında Özofagus Klirensi: Reflü Sintigrafisi ve 24 Saatlik Empedans ve Ph Monitorizasyonunun Refrakter Semptomatik Hastalarda Korelasyonu

Leticia Burton[1], Gregory L. Falk[2], Karl Baumgart[3], John Beattie[4], Scott Simpson[5], Hans Van der Wall[1]

[1]*University of Notre Dame, CNI Molecular Imaging, Sydney, Australia*
[2]*Concord Hospital and University of Sydney, Sydney Heartburn Clinic, Sydney, Australia*
[3]*North Shore Medical Centre, Sydney, Australia*
[4]*Ryde Medical Centre, Sydney, Australia*
[5]*Sydney Adventist Hospital and University of Sydney, Sydney, Australia*

Abstract

Objectives: The role of gastroesophageal reflux disease (GERD) in the aetiology of laryngopharyngeal reflux (LPR) is poorly understood and remains a controversial issue. The 24-hour impedance monitoring has shown promise in the evaluation of LPR but is problematic in pharyngeal recording. We have shown the utility of scintigraphic studies in the detection of LPR and lung aspiration of refluxate. Correlative studies were obtained in patients with a strong history of LPR and severe GERD.

Methods: A highly selected sequential cohort of patients with a high pre-test probability of LPR/severe GERD who had failed maximal medical therapy were evaluated with 24-hour impedance/pH, manometry and scintigraphic reflux studies.

Results: The study group comprised 34 patients (15 M, 19 F) with a mean age of 56 years (range: 28-80 years). The majority had LPR symptoms (mainly cough) in 31 and severe GERD in 3. Impedance bolus clearance and pH studies were abnormal in all patients in the upright and supine position. A high rate of non-acid GERD was detected by impedance monitoring. Lower oesophageal spincter tone and ineffective oesophageal clearance were found in the majority of patients. Scintigraphic studies showed strong correlations with impedance, pH and manometric abnormalities, with 10 patients showing pulmonary aspiration.

Conclusion: Scintigraphic studies appear to be a good screening test for LPR and pulmonary aspiration as there is direct visualisation of tracer at these sites. Impedance studies highlight the importance of non-acidic reflux and bolus clearance in the causation of cough and may allow the development of a risk profile for pulmonary aspiration of refluxate.

Keywords: Gastroesophageal reflux disease, laryngopharyngeal reflux, reflux, impedance, pH, manometry, scintigraphy, pulmonary aspiration

Öz

Amaç: Laringofarengeal reflü (LFR) etiyolojisinde gastroözofageal reflü hastalığının (GÖRH) rolü tam olarak anlaşılamamıştır ve bu durum tartışmalı bir konu olmaya devam etmektedir. Yirmi dört saatlik empedans monitörizasyonu LFR'nin değerlendirilmesinde umut vaat etmektedir, ancak faringeal kayıtlamada sorun yaşanmaktadır. Biz, LFR'nin ve reflünün akciğer aspirasyonunun saptanmasında sintigrafik çalışmaların yararını göstermiştik. Şiddetli LFR ve GÖRH öyküsü olan hastalarda korelasyon çalışmaları yapılmıştır.

Yöntem: Maksimum medikal tedaviye yanıt vermeyen ve ön testte LFR/şiddetli GÖRH olasılığı yüksek saptanan seçilmiş bir hasta grubu; 24 saatlik empedans/pH monitörizasyonu, manometri ve sintigrafik reflü çalışmaları ile değerlendirildi.

Bulgular: Çalışma grubu, 15'i erkek, 19'u kadın olmak üzere 34 hastadan oluşmaktaydı ve yaş ortalaması 56 (28-80) idi. Hastaların 31'inde LFR semptomları (çoğunlukla öksürük) ve 3'ünde şiddetli GÖRH semptomları vardı. Empedans bolus klirensi ve pH çalışmaları, ayakta ve sırtüstü pozisyonda tüm hastalarda anormaldi. Empedans monitörizasyon ile yüksek oranda asidik olmayan GÖRH saptandı. Hastaların çoğunda düşük

Address for Correspondence: Hans Van der Wall MD, University of Notre Dame, CNI Molecular Imaging, Sydney, Australia
Phone: +61 2 9736 1040 **E-mail:** hvanderwall@gmail.com **ORCID ID:** orcid.org/000-0003-4184-3330
Received: 28.06.2019 **Accepted:** 06.10.2019

özofageal sfinkter tonusu ve inefektif özofageal klirens saptandı. Sintigrafik çalışmalar pulmoner aspirasyon gelişen 10 hastada; empedans, pH ve manometrideki anormalliklerle yüksek korelasyon gösterdi.

Sonuç: Sintigrafik çalışmalar, LFR ve pulmoner aspirasyon için iyi bir tarama testi gibi görünmektedir, çünkü bu bölgelerde tracerin doğrudan gösterilmesi mümkündür. Empedans çalışmaları, öksürüğün nedeni olarak asidik olmayan reflü ve bolus klirensinin önemini vurgulamaktadır ve reflünün pulmoner aspirasyonu için bir risk profilinin geliştirilmesinde kullanılabilir.

Anahtar kelimeler: Gastroözofageal reflü hastalığı, laringofarengeal reflü, reflü, empedans, pH, manometri, sintigrafi, pulmoner aspirasyon

Introduction

The pathophysiology of proximal gastrooesophageal reflux disease (GERD) causing laryngopharyngeal reflux (LPR) is poorly understood (1,2). It is an important consideration in the aetiology of chronic cough which remains undiagnosed after eight weeks of specialist investigation (1,2,3,4). The pathophysiology of reflux-induced cough is poorly described and the disease remains in dispute (1,2). Various disease processes may be generators of laryngeal and pharyngeal symptoms including proximal GERD. These may manifest as pharyngeal reflux, laryngeal contamination and pulmonary aspiration as well as acid reflex-mediated bronchospasm (5,6).

Response to proton pump inhibitor (PPI) therapy has been utilised as a diagnostic test (7,8) as there has been no accurate diagnostic test for LPR by which to make the initial diagnosis and to interrogate the success of treatment. A high placebo response in treatment of cough makes the matter more complex when evaluating therapy (7). Investigation of this situation by 24-hour pH reflux testing has been bedevilled by artefacts in the pharynx (9), leading to attempts to modify instrumentation to increase accuracy and reproducibility. The newer technology of reflux impedance monitoring has shown potential to identify non-acidic and slightly acidic reflux episodes as well as pharyngeal contamination (9,10). Intra-observer variability however has been a problem for accuracy of pharyngeal readings (10,11). Identifying reflux high in the oesophagus where observations are more accurate than in the pharynx does not necessarily predict pharyngeal exposure, as the upper oesophageal sphincter separates the chambers. The issue of an episode of reflux changing acidity during ascent in the oesophagus confounds proximal pH measurements, as does the recognition of symptoms associated with non-acid reflux (10,12).

Reflux scintigraphy has been utilised in children and to a variable extent in adults to evaluate pharyngeal contamination and pulmonary aspiration of refluxate (13,14,15). There have however been multiple technical difficulties and a lack of standardisation between studies with variable and sometimes contradictory results (13,16,17,18). We have developed and validated a consistent scintigraphic technique for the detection of GERD and LPR with good correlations with pH monitoring and manometry (19,20).

We hypothesised that scintigraphic reflux studies could provide additional information and complement 24-hour pH and impedance studies in patients with GERD and suspected LPR. A secondary purpose of the study was to evaluate impedance reflux studies in prediction of proximal reflux disease causing LPR symptoms and lung aspiration of refluxate.

Materials and Methods

Clinical

Consecutive patients failing adequate medical investigation and management, with a high pre-test probability of proximal GERD with LPR symptoms were referred to a tertiary anti-reflux surgical service in the past 3 years. Patients underwent standard symptom pro-forma interview with regard to LPR symptoms including amongst others, cough, sore throat, voice change, and dyspnoea. Patients had previously undergone gastroscopy and laryngoscopy for symptoms of GERD/LPR. Alternative causes of LPR symptoms had been excluded by multi-disciplinary investigations.

Manometry, 24-hour dual channel pH and impedance reflux and scintigraphic reflux studies were obtained in all patients while off PPI therapy.

Hiatus hernia was diagnosed by endoscopy.

Oesophageal manometry was performed under topical nasal anaesthesia using a dent sleeve 4 mm trans-nasal 6 lumen catheter placed by identification of the lower oesophageal sphincter (LOS) by pull through and placement of the sleeve in the LOS. Wet swallows (10) of 2.5 mL water were performed by stationary technique using the dent mark 2 infusion pump (Dentsleeve International Ltd., Mississauga, Ontario, Canada). Studies were performed in the supine position. The swallows were assessed for peristaltic efficacy (21) and sphincter characteristics were determined. A lesser sub-group of motility disturbance was created for 20-30% ineffective oesophageal motility (IEM) which would previously have been included in the normal

group. Resting pressure of the sphincter and nadir pressure were reported from the mid-end expiratory pressure.

Twenty four-hour impedance reflux study with two channel 24-hour pH was performed after cessation of all anti-acid therapy for 48 hours. Patients were prepared with local anaesthetic prior to insertion of a trans-nasal catheter consisting of 2 level impedance rings and 2 level pH electrodes connected to an external monitoring device. Standard calibration was carried out. Impedance rings were placed at 5 and 15 cm above the upper border of the LOS (Zephyr device, catheter ZAI-BD31, Sandhill Co, Highlands Ranch, Colorado, USA). There were no dietary restrictions during the testing period other than ingestions of acidic beverages. Catheter placement was ascertained by measurements taken at manometry with the lower pH electrode 5 cm above the upper border of the LOS, the upper, 15 mm higher. The patient returned the following day when the assembly was removed. Meal-times were included in the reporting analysis. Reports of 24-hour pH and 24-hour impedance reflux were then generated using autoscan and manual review. Events which were considered not to be reflux or indeterminate were excised from the report. The categories of reflux were classified according to the consensus on impedance and pH monitoring (22). Briefly, it was based on oesophageal pH during reflux detected by impedance monitoring. Acid reflux was a fall in pH below 4, weakly acid reflux was a fall in pH which was ≥4 but <7 and non-acid reflux where oesophageal pH increases ≥7 or remained ≥7 during reflux. Liquid bolus entry was the time when the 50% fall in impedance from baseline during liquid reflux was reached. Bolus duration was the time from liquid bolus entry to liquid bolus clearance (impedance increasing for >5 seconds).

Scintigraphy

Patients were fasted for 12 hours and medications were ceased for the 24-hours prior to the test. While upright, patients were positioned in front of a Hawkeye 4 gamma camera (General Electric, Milwaukee, USA) with markers placed on the mandible and over the stomach to ensure the regions of interest were within the field of view of the camera. Patients swallowed 100-150 mL of water with 40-60 MBq of 99mTc diethylenetriamine penta-acetic acid followed by flushing with 50 mL of water to clear the mouth and oesophagus of radioactivity. Dynamic images of the pharynx, oesophagus and stomach were obtained for 5 minutes at 15 secs per frame into a 64x64 matrix. A second 30-minute dynamic image was obtained in the supine position immediately following the upright study utilising 30 sec frames (Figure 1). Following acquisition of the supine study, the patients were given a further 50 mL of water with 60 MBq of 99mTc phytate (colloid) followed by 50 mL of water as a flush. Delayed images were obtained at 2 hours to assess the presence of aspiration of tracer activity into the lungs. Images were analysed by time activity curves over the pharynx, upper and lower half of the oesophagus and a background region over the right side of the chest, away from the stomach and oesophagus (Figure 2). Delayed images were analysed by a line profile over the lungs. Time activity curves were graded as showing no GERD, a falling curve, flat or rising curves. Area under the curve and maximal amplitude relative to background were estimated. A liquid gastric emptying half-time was

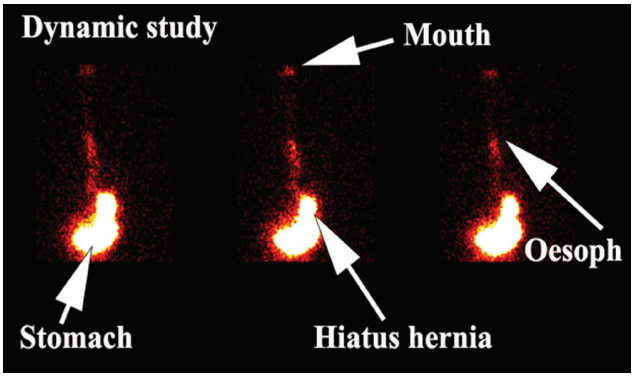


Figure 1. Dynamic scintigraphic study. The sequence of images demonstrates tracer activity in the stomach with evidence of a hiatus hernia and gastro-oesophageal reflux to the level of the oropharynx. Note the progressive accumulation of tracer in the region of the oropharynx (mouth)

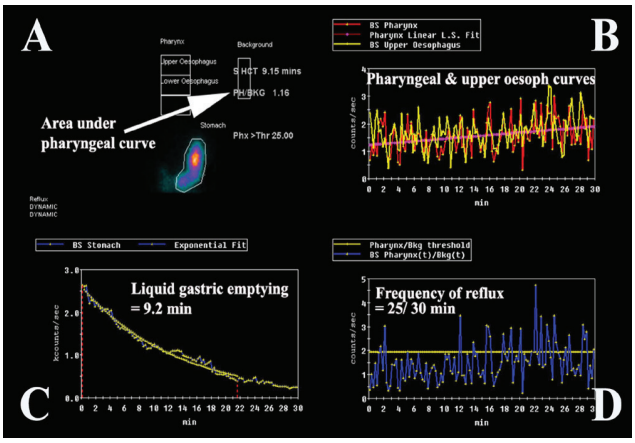


Figure 2. Graphical analysis of the dynamic study. (A) This panel demonstrates the regions of interest over the pharynx, upper and lower oesophagus with the background region of interest. It also indicates the area under the pharyngeal curve. Panel (B) illustrates the graphical output from the region of interest over the pharyngeal/laryngopharyngeal and upper oesophageal areas with the fitted pink curve demonstrating a rising pattern for the pharyngeal region. Panel (C) shows the analysis of the supine dynamic study of the liquid gastric emptying time. Panel (D) shows the frequency of reflux to the level of the pharynx/laryngopharynx with the fitted yellow line indicating the residual level after subtraction of background activity

determined from the 30-minute supine acquisition with a single exponential fit to the data.

Ethical Considerations

Patient data were extracted from a research database of either proven or suspected GERD which had been approved by the Institutional Ethics Committee of Concord Hospital (LNR/12CRGH/248). Patients gave written informed consent for the study under the Institutional Ethics Committee Guidelines.

Statistical Analysis

All statistics were calculated using the Statistical Package for the Social Sciences Version 24 (IBM, New York, USA). A proportion of the data was non-parametric in nature with ordinal responses such as the isotope time-activity curves for the pharynx and upper oesophagus (Grade 1-3) and lung aspiration of isotope (1=positive, 0=negative). All other variables were parametric or continuous. Spearman rank-order correlation was used for the non-parametric data and Pearson correlation co-efficient was used for the parametric data analysis. The paired t-test was utilised for comparison of test results in the same patient. Binary logistic regression and receiver operating characteristic (ROC) curves were utilised for determining best predictors of lung aspiration of refluxate.

Results

Clinical

Results were obtained from 34 consecutive patients undergoing impedance pH/manometric studies and compared with scintigraphic reflux studies. This comprised 15 males and 19 females (mean age 56 years, range 28-80 years). The dominant symptoms were of LPR (mainly cough) in 31 and severe typical GERD in 3 cases. The predominant symptom was cough which occurred in 27, other LPR symptoms were recorded in 4, heartburn and regurgitation in 3. Twenty patients were taking PPI, which were ceased for 48 hours prior to testing. No significant differences in results were recorded for the patients taking PPI and those not on PPIs.

A hiatus hernia was present in 16 patients. There was no significant correlation between hiatus hernia and impedance/pH results, manometric or scintigraphic parameters.

Impedance and pH

Impedance bolus clearance (Figure 3) when upright was a mean of 17.5 [range: 6-42, standard deviation (SD): 7.5] for this population. Results in normal volunteers have been reported as a median of 8 (95% value of 31) (23). Impedance bolus clearance for the 34 patients when supine was a mean of 25.1 (range: 0-214, SD: 34.4), compared to a values of 1-7 in normal volunteers (23). Impedance bolus clearance in total was a mean of 21.1 (range: 8-35, SD: 6.7).

pH results are provided in Tables 1 and 2. The means for acid, non-acid and total proximal reflux were significantly greater than has been reported in normal volunteers by Shay et al. (23). Even the relatively common occurrence of upright reflux in normal volunteers (mean 1.2%) was significantly higher in this group (mean ~ 10% for acid and non-acid reflux). The frequency of supine reflux at the proximal and distal sites in the oesophagus was markedly

Table 1. Proximal reflux by pH monitoring

	Acid			Non-acid			Total reflux		
	Mean	Range	SD	Mean	Range	SD	Mean	Range	SD
Upright	9.4	0-44	11.6	11.8	0-45	10.3	22.4	2-79	15.1
Supine	1.4	0-10	2.4	1.5	0-14	2.7	2.9	0-24	4.6
All reflux	10.6	0-44	12.2	13.3	2-47	11.7	23.9	2-83	17.2

SD: Standard deviation

Table 2. Distal reflux by pH monitoring

	Acid			Non-acid			Total reflux		
	Mean	Range	SD	Mean	Range	SD	Mean	Range	SD
Upright	17.4	0-70	21.0	20.5	0-90	22.6	40.2	9-117	25.1
Supine	4.6	0-72	13.6	3.1	0-16	4.0	8.9	0-74	13.8
All reflux	22.0	0-127	29.2	28.7	4-102	25.6	49.1	10-131	31.7

SD: Standard deviation

greater by an order of magnitude than in normal volunteers (24).

There was no significant difference between proximal acid event frequency and proximal non-acid event frequency in either the upright or supine position by the paired t-test. There was no correlation between any markers of distal pH and either LPR or lung aspiration in the scintigraphic studies.

Manometric Characteristics of the Group

The LOS pressure was a mean of 2.0 mmHg (range: 0-12, SD: 2.8) compared with a normal sphincter pressures ranging from 18 to 25 mmHg. Thirty patients in this group had a hypotensive LOS. Sphincter pressure was not recorded in 4 patients due to technical difficulty: One patient could not tolerate it and we were unable to traverse the sphincter region in 3 others. Normal oesophageal body motility was present in 4 patients, 9 had a mild non-specific IEM, 4 had moderate IEM and 17 severe IEM according to our modification of the Kahrilas classification (21), where we separated mildly abnormal from normal patients which were included under the normal umbrella in that study.

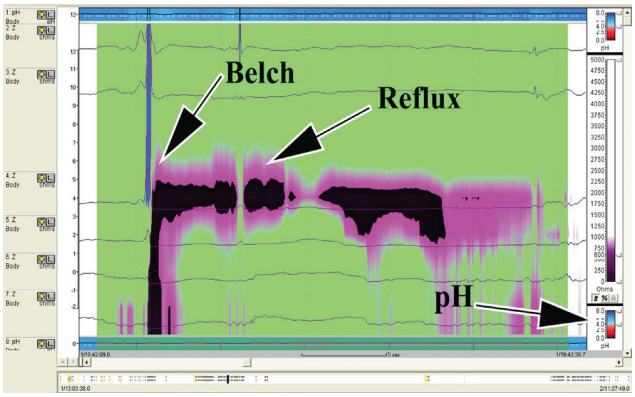


Figure 3. Impedance study demonstrating significant gastro-oesophageal reflux following a belch and the rapid fall in pH and impedance as acid/fluid enters the oesophagus. There is prolongation in clearance of the acid/fluid from the oesophagus (reflux). The pink colour is a marker of the acidity as shown in the colour bar (pH)

Table 3. Scintigraphic curve analysis

Dominant symptom profile	Curve analysis for pharynx/laryngopharynx			
	Grade 1	Grade 2	Grade 3	Aspiration
GERD upright	0	2	1	1
GERD supine	0	2	1	
LPR upright	5	10	16	9
LPR supine	4	5	22	

GERD: Gastro-esophageal reflux disease, LPR: Laryngopharyngeal reflux

Scintigraphy

All 34 patients showed scintigraphic evidence of gastroesophageal regurgitation events and nasopharyngeal contamination in either the upright or supine position or both. A rising or flat time-activity curve was apparent for the pharynx in 30/34 and for the upper oesophagus in 25/34 cases (Table 3). The mean amplitude of activity in the pharynx when compared to background activity of the right upper lung and expressed as a ratio was 4.4 [95% confidence interval (CI): 3.7-5.1].

Pulmonary aspiration of refluxate was apparent in 10 of 34 cases. Of these, 9 patients had atypical histories and 1 had a typical history of heartburn and regurgitation. The most common symptoms associated with aspiration were cough, choking and recurrent throat clearing.

Liquid gastric emptying was abnormal in 12/34 cases (T1/2>16 min). Mean of the abnormal cases was 30 min (95% CI: 15-45 min). There was no significant relationship between liquid gastric emptying and any other scintigraphic results including LPR or lung aspiration of refluxate.

Statistical Correlations

Impedance and scintigraphy (Table 3).

Clearance of refluxate from the oesophagus (impedance bolus clearance) was inversely correlated with the isotope pharyngeal time-activity curves. The longer time to clear the oesophagus of refluxate and return impedance to normal was associated with an increased likelihood of scintigraphic pharyngeal contamination by refluxate and a rising level of refluxate activity in the pharynx in the upright and supine positions (Spearman correlation co-efficient -0.38, $p<0.05$): Similarly, impaired clearance was strongly associated with increased isotope identification in the upper oesophagus (Spearman correlation co-efficient 0.60, $p<0.05$). Abnormal gastric emptying appeared to have no association with abnormal oesophageal clearance. There was a strong positive association of all measures of increasing bolus clearance duration and findings of isotope pulmonary aspiration (Spearman correlation co-efficient 0.38-0.60, $p<0.05$).

Binary logistic regression analysis of pulmonary aspiration found that the best predictor of pulmonary aspiration was the delay in impedance bolus clearance when upright (wald 4.25, $p=0.039$). Other findings in pH, manometry and scintigraphy did not predict pulmonary aspiration (Table 4).

The best predictor of aspiration of refluxate into the lungs are the upright bolus clearance and total bolus clearance in the impedance studies. This is shown in the receiver operating characteristic curve in Figure 4.

pH and Scintigraphy

Isotope amplitude in the pharynx was positively correlated with non-acid proximal reflux when supine (Pearson correlation co-efficient 0.35, p=0.04) and all proximal supine reflux (Pearson correlation co-efficient 0.38, p=0.03). A rising curve for the upper oesophagus was associated with significant proximal oesophageal acid exposure. Non-acid proximal reflux when supine was positively correlated with pulmonary aspiration in the scintigraphic studies (Spearman correlation co-efficient 0.36, p=0.04). Proximal acid reflux in the upright or supine position did not correlate with either scintigraphic pharyngeal exposure or lung aspiration of refluxate.

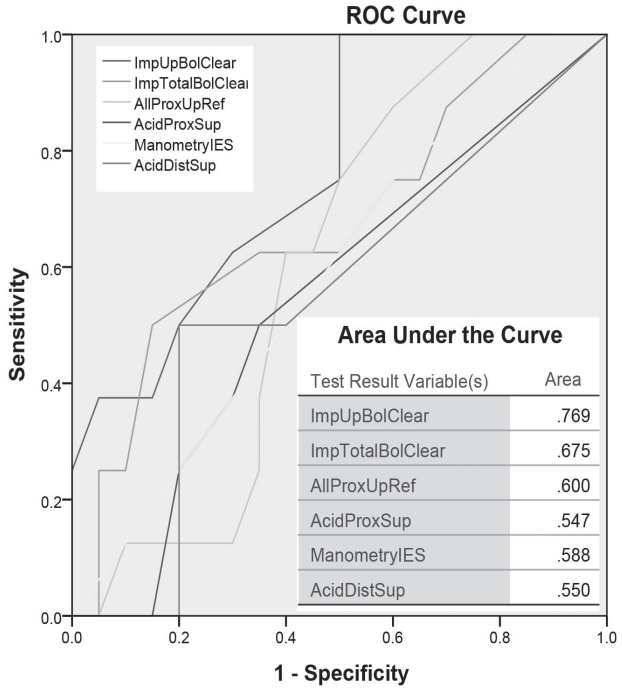


Figure 4. Receiver operating characteristic curve. The curve examines the best predictor of lung aspiration of refluxate amongst the standard testing methods of impedance, manometry and pH studies. The value is based on the comparison of areas under the curve in the interplay between sensitivity and specificity. In this instance, the best predictor of aspiration of refluxate into the lungs are the upright bolus clearance and total bolus clearance in the impedance studies. Note that the least useful value is the acid exposure of the proximal and distal oesophagus in the supine position
ROC: Receiver operating characteristic

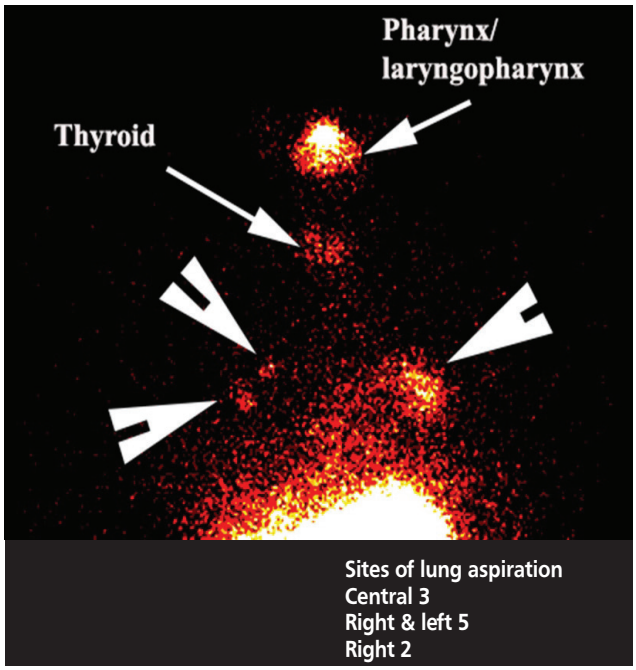


Figure 5. Bilateral lung aspiration. The arrowheads show sites of lung aspiration of refluxate into the main airways in both lungs. Note activity in the pharynx/laryngopharynx and some breakdown of the phytate with free pertechnetate uptake in the thyroid gland (arrows). The Table shows the sites of aspiration which are invariably in the central aspects of both lungs rather than in the lung bases

Table 4. Correlations: Impedance-pH and scintigraphy

Significant correlations	p	Corr	No significant correlations	p	Corr
Isotope amplitude/supine prox non-acid reflux	0.041	0.35 PCC	Isotope pharyngeal curve/total prox reflux	>0.05	-0.18 Spear
Isotope amplitude/supine total prox reflux	0.029	0.38 PCC	Isotope pharyngeal curve/supine total prox reflux	>0.05	-0.23 Spear
Isotope pharyngeal curve/upright Imp bolus clear	<0.05	-0.36 Spear	Isotope pharyngeal curve/supine Imp bolus clear	0.05	-0.13 Spear
Isotope pharyngeal curve/total Imp bolus clear	0.00	-0.42 Spear	Isotope amplitude/total Imp bolus clearance	0.88	0.028 PCC
Isotope aspiration/upright Imp bolus clear	<0.05	0.38 Spear	Isotope aspiration/total Imp bolus clear	>0.05	0.27 Spear
Upper oesophageal curve/total Imp bolus clearance	<0.05	-0.60 Spear	Upper oesophageal curve/supine Imp bolus curve	>0.05	-0.046 Spear

p: p value, PCC: Pearson correlation, Spear: Spearman, Corr: Correlation, Imp: Impedance

Figure 4 shows that acid exposure in the upper oesophagus was not a good predictor of aspiration of refluxate in the lungs.

Manometry and Impedance/pH (Reflux/Clearance)

LOS pressure correlated with decreased impedance bolus clearance in the upright position (Pearson correlation co-efficient 0.36, p=0.04) but not in the supine position or with total bolus clearance (Table 5).

A strong correlation was found between decreased manometric LOS pressure and increase in total proximal supine reflux event frequency (Pearson correlation co-efficient 0.58, p=0.001). Total proximal upright reflux event frequency was also correlated with worsening ineffective oesophageal clearance by manometry (Pearson correlation co-efficient 0.40, p=0.02). No significant difference was found between patients with normal oesophageal clearance and those with mild clearance abnormalities and this may be due to inadequate numbers of patients with normal clearance (n=4) leading to a type 1 error.

Manometry and Scintigraphy

LOS pressure was inversely correlated with isotope amplitude in the laryngopharynx (Pearson correlation co-efficient -0.37, p=0.04) but not with any other scintigraphic variable such as lung aspiration (Table 5).

Discussion

It is important to state from the outset that the population in this study had severe established gastro-oesophageal reflux disease which was referred to a tertiary centre for consideration of laparoscopic fundoplication, largely after exclusion of other diseases by multiple other disciplines. Nearly all patients had both symptoms and investigative findings consistent with LPR disease. This group was characterized by the failure of response to high-dose PPI therapy. Approximately half the patients had hiatus hernias and the majority, abnormalities of LOS pressures. There was clearly a high susceptibility to high-grade reflux disease in this group of patients as has been reported previously (20).

Patients were studied with impedance/pH, manometry and scintigraphic reflux studies. The principal purpose of the studies was assessment for surgery, but these studies have enabled evaluation of the relative contributions of impedance monitoring and standard pH monitoring to predict LPR and lung aspiration of reflux detected by scintigraphic studies, which we have validated in previous work (19,20).

The most outstanding findings in the standard manometric studies was the LOS pressure which was a mean of 2 mmHg compared with a normal range of 18-25 mmHg. Only 4 of 34 patients had normal oesophageal motility underlining the degree of oesophageal clearance abnormalities in this population.

Impedance/pH studies allowed the evaluation of total reflux events (acid + non-acid) in the upper and lower oesophagus in a group of patients in whom PPI and other antacid therapy had been ceased prior to the study. Total proximal reflux measured by the impedance studies was found to be significantly different from both acid (measured by pH probe) and non-acid reflux (measured by impedance probe), reflecting the inadequacy of isolated pH monitoring as a tool for detection of proximal reflux. This is particularly problematic for detection of proximal non-acid reflux which may be significantly more common than acidic reflux (25), given that there is progressive neutralisation of gastric contents as refluxate ascends the oesophagus to its proximal extent or that primary reflux may be non-acidic or even alkaline in patients on maintenance PPI therapy (26,27).

All patients in this study were tested while off PPI therapy. In the study by Mainie et al. (27) on patients with symptoms refractory to PPI therapy (n=144), it was shown that non-acid reflux occurred in 37% and acid reflux in 11% utilising impedance/pH monitoring while still on PPI therapy. In line with these findings was the inverse correlation between LOS pressure and bolus clearance when the patient was upright. It indicates that the severity of abnormal dynamics in the oesophagus cannot be overcome by even favourable

Table 5. Correlations: Manometry and scintigraphy/Impedance-pH

Significant correlations	p	Corr	No significant correlations	p	Corr
Manometric lower oesophageal sphincter presssure/isotope amplitude	0.0.042	0.37 PCC	Manometric lower oesophageal sphincter presssure Isotope pharyngeal curve	<0.05	-0.21 Spear
Manometric lower oesophageal sphincter presssure/supine proximal total reflux	0.001	0.58 PCC	Manometric lower oesophageal sphincter presssure/isotope aspiration	<0.05	-0.11 Spear
Manometric ineffective oesophageal clearance/ upright total proximal reflux	0.02	0.40 PCC	Manometric ineffective oesophageal clearance/total proximal reflux	0.20	0.25 PCC

p: p value, PCC: Pearson correlation, Spear: Spearman, Corr: Correlation

gravitational circumstances. A strong positive correlation was also found between total proximal supine reflux event frequency (by impedance probe) and ineffective oesophageal clearance. Not only does the LOS pressure allow free reflux by a mechanical dysfunction but the associated motility disturbance fails to clear the refluxate from the oesophagus. There is a wealth of literature supporting this observation (28,29,30). Impedance bolus transit abnormalities parallel the severity of GERD (31) and in our study showed a significant correlation with a rising upper oesophageal scintigraphic time-activity curve. Under normal circumstances, clearance occurs as a function of gravity and peristalsis with neutralisation of acid by swallowed saliva (30).

The importance of non-acid GERD triggering symptoms has been a vexed issue which has been directly addressed by impedance studies. As the study of Mainie et al. (27) has shown, non-acidic reflux remains a cause of symptoms in patients on high-dose twice daily PPI therapy. Not all patients with non-acidic GERD have symptoms, even patients with established LPR and lung aspiration of refluxate may not have symptoms (20). The lack of symptoms implies a clinically silent but potentially damaging phenomenon and raises the question of appropriate therapy. A number of strategies have been advocated including agents that inhibit transient relaxation of the LOS (32) and experimental endoscopic therapies (26). Ultimately, surgical treatment with laparoscopic fundoplication has efficacy that has been established in numerous studies (19,33,34,35) on the basis of pH monitoring alone and more recently, impedance/pH monitoring in patients with non-acid but symptomatic GERD (36,37).

What additional value does the scintigraphic reflux study contribute to such a group of patients? Impedance and pH studies interrogate both the distal and proximal oesophagus for significant gastro-oesophageal reflux, be it acidic or non-acidic. Distal single-channel 24-hour pH does not show proximal reflux disease as has been shown in this study and dual-channel 24-hour pH is confounded by neutralisation of reflux during ascent of the oesophagus. The combined study assesses the severity and frequency of reflux, forming the basis of principles for treatment. However, the relatively uninterpretable areas that are not reproducibly identified in pharyngeal recording by the combined technique are the laryngopharynx and aspiration of refluxate into the lungs. While there has been some evidence of the utility of impedance studies in the detection of laryngopharyngeal reflux, issues of reproducibility in the pharynx are a significant problem with the current generation of instruments (11). The newer generation of impedance instruments may overcome this problem.

Scintigraphic studies allow direct visualisation of the entry of refluxate into the nasopharyngeal region as a dynamic study in cine format in the upright and supine position (Figure 1). It illustrates whether such activity is rising, static or clearing (Figure 2). We have shown in previous work that a rising pharyngeal curve is highly predictive of lung aspiration of refluxate (19). The delayed study shows if there has been aspiration of tracer into the lungs, which are normally free of tracer activity.

Scintigraphic studies are a good screening tool but as the sampling time is approximately 33 minutes in total, do not give an actual idea of the overall frequency of GERD, as do the 24-hour recordings of impedance/pH (Figure 3) and manometry. It may well underestimate the frequency and extent of reflux. There is however the clear implication that if such activity is visualised in 30 minutes, under conditions that do not predispose to reflux such as stomach filling as occurs after meals, then it reflects a chronicity of recurrence. Aspiration is screened for at 2 hours (Figure 5). Previous experience with 12-24-hour screening has not added to the pick-up rate significantly and was though not to justify the inconvenience of bringing patients back for a second time. The study has a low radiation dose, being less than a chest X-ray and is relatively non-invasive as the patient swallows approximately 100 mL of radioactive liquid (40-60 MBq). The study is non-invasive and relatively inexpensive to obtain.

All 34 patients showed scintigraphic evidence of pharyngeal contamination with approximately one third aspirating refluxate into the lungs (Figure 5). This is a consistent pattern that we have observed in a previous study of patients undergoing laparoscopic fundoplication for symptomatic GERD and LPR which was resistant to high-dose PPI therapy (19). Time activity curves for the lower pharynx/laryngopharynx and the area under the curve are obtained from a region of interest positioned below retained activity in the oropharynx from the initial swallow (Figure 2). These derived markers of reflux therefore reflect an integration of the volume of reflux and failure of adequate clearance and is an effective parallel of the impedance marker of bolus clearance. The time-activity curves for the region showed a good correlation with the impedance findings of delayed bolus clearance from the oesophagus. The greater the delay in bolus clearance, the more likely was a rising time-activity curve for the lower pharynx/laryngopharynx. Furthermore, the increasing delay in bolus clearance made the chance of pulmonary aspiration much higher. Logistic regression identified the

delay in upright bolus clearance as the only factor that predicted pulmonary aspiration of refluxate (Figure 4). This may be an underestimate of supine aspiration, given that aspiration scanning was performed after a period of upright delay, rather than after lying supine for a longer period, as would occur during sleep.

Isotope amplitude is a measure of the highest single reflux episode compared to background activity. It is not a manifestation of "noise" on the curve as it is consistently shown on the curve obtained from the mid/lower oesophagus region of interest in the same temporal sequence. Isotope amplitude for the degree of refluxate in the lower pharynx/laryngopharynx was inversely correlated with LOS pressure and rose with falling pressures. It was also strongly correlated with non-acidic reflux and all reflux in the supine position. Pulmonary aspiration of refluxate was strongly correlated with proximal non-acidic reflux when the patient was supine, suggesting that sleep or the lack of sensory stimulus of less acidic material may disable protective reflex mechanisms (38). Such findings will allow the derivation of a risk-profile that allows prediction of the likelihood of LPR and lung aspiration of refluxate. In contrast, proximal acid reflux did not correlate with either lower pharyngeal/laryngopharyngeal amplitude or aspiration of tracer, again underlining the inherent inability of pH studies in identifying a risk profile for LPR and lung aspiration of refluxate.

Conclusion

A surprising level of ineffective oesophageal clearance has been identified in this series suggesting that oesophageal body dysfunction is a factor in proximal progression of refluxate. The advent of impedance studies has changed the paradigm for screening patients for GERD. It has brought the issue of non-acidic reflux into focus and increased the understanding of how symptoms can persist while patients are on maintenance high-dose PPI therapy. Many of the findings of oesophageal clearance are well correlated with the scintigraphic reflux studies and allow the formulation of a risk profile for the occurrence of LPR and lung aspiration of refluxate. Scintigraphic reflux studies are a good screening tool for reflux as they also demonstrate extra-oesophageal manifestations in the head, neck and lungs which is spectacularly shown by single photon emission computed tomography fused with low-dose X-ray computed tomography. We have found that LPR and lung aspiration of refluxate can only be attenuated or ceased by surgical fundoplication. Our experience in over 50 cases on maximal medical therapy is that the symptoms may disappear, but LPR and lung aspiration do not.

Ethics

Ethics Committee Approval: Patient data were extracted from a research database of either proven or suspected GERD which had been approved by the Institutional Ethics Committee of Concord Hospital (LNR/12CRGH/248).

Informed Consent: Patients gave written informed consent for the study under the Institutional Ethics Committee Guidelines.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Data Collection or Processing: L.B., G.L.F., Analysis or Interpretation: L.B., Literature Search: L.B., G.L.F., K.B., J.B., S.S., H.V.W., Writing: L.B.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Navaratnam RM, Winslet MC. Gastro-oesophageal reflux: the disease of the millennium. Hosp Med 1998;59:646-649.
2. Spechler SJ. Laryngopharyngeal reflux: a cause of faulty phonation or a faulted, phony diagnosis? Clin Gastroenterol Hepatol 2006;4:431-432.
3. Vaezi MF. Review article: the role of pH monitoring in extraoesophageal gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2006;23(Suppl 1):40-49.
4. Vaezi MF. Laryngeal manifestations of gastroesophageal reflux disease. Curr Gastroenterol Rep 2008;10:271-277.
5. Ing AJ. Cough and gastro-oesophageal reflux disease. Pulm Pharmacol Ther 2004;17:403-413.
6. Smith JA, Abdulqawi R, Houghton LA. GERD-related cough: pathophysiology and diagnostic approach. Curr Gastroenterol Rep 2011;13:247-256.
7. Faruqi S, Molyneux ID, Fathi H, Wright C, Thompson R, Morice AH. Chronic cough and esomeprazole: a double-blind placebo-controlled parallel study. Respirology 2011;16:1150-1156.
8. Shaheen NJ, Crockett SD, Bright SD, Madanick RD, Buckmire R, Couch M, Dellon ES, Galanko JA, Sharpless G, Morgan DR, Spacek MB, Heidt-Davis P, Henke D. Randomised clinical trial: high-dose acid suppression for chronic cough - a double-blind, placebo-controlled study. Aliment Pharmacol Ther 2011;33:225-234.
9. Hoppo T, Komatsu Y, Jobe BA. Antireflux surgery in patients with chronic cough and abnormal proximal exposure as measured by hypopharyngeal multichannel intraluminal impedance. JAMA Surg 2013;148:608-615.
10. Shay SS, Abreu SH, Tsuchida A. Scintigraphy in gastroesophageal reflux disease: a comparison to endoscopy, LESp, and 24-h pH score, as well as to simultaneous pH monitoring. Am J Gastroenterol 1992;87:1094-1101.
11. Zerbib F, Roman S, Bruley Des Varannes S, Gourcerol G, Coffin B, Ropert A, Lepicard P, Mion F; Groupe Français De Neuro-Gastroentérologie. Normal values of pharyngeal and esophageal 24-hour ph impedance in individuals on and off therapy and interobserver reproducibility. Clin Gastroenterol Hepatol 2013;11:366-372.
12. Vela MF. Non-acid reflux: detection by multichannel intraluminal impedance and pH, clinical significance and management. Am J Gastroenterol 2009;104:277-280.

13. Kjellen G, Brudin L, Hakansson HO. Is scintigraphy of value in the diagnosis of gastrooesophageal reflux disease? Scand J Gastroenterol 1991;26:425-430.
14. Maurer AH, Parkman HP. Update on gastrointestinal scintigraphy. Semin Nucl Med 2006;36:110-118.
15. Ravelli AM, Panarotto MB, Verdoni L, Consolati V, Bolognini S. Pulmonary aspiration shown by scintigraphy in gastroesophageal reflux-related respiratory disease. Chest 2006;130:1520-1526.
16. Caglar M, Volkan B, Alpar R. Reliability of radionuclide gastroesophageal reflux studies using visual and time-activity curve analysis: inter-observer and intra-observer variation and description of minimum detectable reflux. Nucl Med Commun 2003;24:421-428.
17. Seymour JC, West JH, Drane WE. Sequential ten-second acquisitions for detection of gastroesophageal reflux. J Nucl Med 1993;34:658-660.
18. Tuncel M, Kiratli PO, Aksoy T, Bozkurt MF. Gastroesophageal reflux scintigraphy: interpretation methods and inter-reader agreement. World J Pediatr 2011;7:245-249.
19. Falk GL, Beattie J, Ing A, Falk SE, Magee M, Burton L, Van der Wall H. Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? World J Gastroenterol 2015;21:3619-3627.
20. Falk M, Van der Wall H, Falk GL. Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms. Nucl Med Commun 2015;36:625-630.
21. Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A. Esophageal peristaltic dysfunction in peptic esophagitis. Gastroenterol 1986;91:897-904.
22. Sifrim D, Castell D, Dent J, Kahrilas PJ. Gastro-oesophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut 2004;53:1024-1031.
23. Shay S, Tutuian R, Sifrim D, Vela M, Wise J, Balaji N, Zhang X, Adhami T, Murray J, Peters J, Castell D. Twenty-four hour ambulatory simultaneous impedance and pH monitoring: a multicenter report of normal values from 60 healthy volunteers. Am J Gastroenterol 2004;99:1037-1043.
24. Sloan S, Rademaker AW, Kahrilas PJ. Determinants of Gastroesophageal Junction Incompetence: Hiatal Hernia, Lower Esophageal Sphincter, or Both? Ann Intern Med 1992;117:977-982.
25. Tolin Hernani M, Crespo Medina M, Luengo Herrero V, Martínez López C, Salcedo Posadas A, Alvarez Calatayud G, Morales Pérez JL, Sánchez Sánchez C. Comparison between conventional pH measurement and multichannel intraluminal esophageal impedance in children with respiratory disorders. Ann Pediatr (Barc) 2012;77:103-110.
26. Mainie I, Tutuian R, Castell DO. The limitations of pH monitoring for detecting gastroesophageal reflux. Clin Gastroenterol Hepatol 2006;4:1184.
27. Mainie I, Tutuian R, Shay S, Vela M, Zhang X, Sifrim D, Castell DO. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. Gut 2006; 55:1398-1402.
28. Chen CL, Yi CH, Liu TT. Heterogeneity in oesophageal dysfunction among patients with different reflux symptoms. Eur J Gastroenterol Hepatol 2012;24:1059-1065.
29. Fornari F, Blondeau K, Durand L, Rey E, Diaz-Rubio M, De Meyer A, Tack J, Sifrim D. Relevance of mild ineffective oesophageal motility (IOM) and potential pharmacological reversibility of severe IOM in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2007;26:1345-1354.
30. Simren M, Silny J, Holloway R, Tack J, Janssens J, Sifrim D. Relevance of ineffective oesophageal motility during oesophageal acid clearance. Gut 2003;52:784-790.
31. Savarino E, Gemignani L, Pohl D, Zentilin P, Dulbecco P, Assandri L, Marabotto E, Bonfanti D, Inferrera S, Fazio V, Malesci A, Tutuian R, Savarino V. Oesophageal motility and bolus transit abnormalities increase in parallel with the severity of gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2011;34:476-486.
32. Vela MF, Tutuian R, Katz PO, Castell DO. Baclofen decreases acid and non-acid post-prandial gastro-oesophageal reflux measured by combined multichannel intraluminal impedance and pH. Aliment Pharmacol Ther 2003;17:243-251.
33. Bell RC, Hanna P, Brubaker S. Laparoscopic fundoplication for symptomatic but physiologic gastroesophageal reflux. J Gastrointest Surg 2001;5:462-467.
34. Chen RY, Thomas RJ. Results of laparoscopic fundoplication where atypical symptoms coexist with oesophageal reflux. Aust N Z J Surg 2000;70:840-842.
35. Pessaux P, Arnaud JP, Delattre JF, Meyer C, Baulieux J, Mosnier H. Laparoscopic antireflux surgery: five-year results and beyond in 1340 patients. Arch Surg 2005; 140:946-951.
36. del Genio G, Tolone S, del Genio F, Aggarwal R, d'Alessandro A, Allaria A, Rossetti G, Brusciano L, del Genio A. Prospective assessment of patient selection for antireflux surgery by combined multichannel intraluminal impedance pH monitoring. J Gastrointest Surg 2008;12:1491-1496.
37. Mainie I, Tutuian R, Agrawal A, Adams D, Castell DO. Combined multichannel intraluminal impedance-pH monitoring to select patients with persistent gastro-oesophageal reflux for laparoscopic Nissen fundoplication. Br J Surg 2006;93:1483-1487.
38. Smith J, Woodcock A, Houghton L. New developments in reflux-associated cough. Lung 2010;188(Suppl 1):81-86.

Original Article
Mol Imaging Radionucl Ther 2018;27:113-120 DOI:10.4274/mirt.10438

Benchmarking of a Simple Scintigraphic Test for Gastro-oesophageal Reflux Disease That Assesses Oesophageal Disease and Its Pulmonary Complications

Basit Bir Sintigrafik Yöntemi Gastro-Özofageal Reflüde Özofagus Hastalığı ve Pulmoner Komplikasyonların Değerlendirme Amaçlı İncelenmesi

Leticia Burton[1], *Gregory L. Falk*[2], *Stephen Parsons*[3], *Mel Cusi*[4], *Hans Van Der Wall*[4]
[1]*CNI Molecular Imaging, Sydney, Australia*
[2]*Sydney Heartburn Clinic, Sydney, Australia*
[3]*University of New South Wales, Sydney, Australia*
[4]*University of Notre Dame, Sydney, Australia*

Abstract

Objectives: Gastro-oesophageal reflux disease (GORD) is both common and troubling with a prevalence of 20-40%. We assessed the utility of a scintigraphic reflux study to evaluate the oesophageal and extra-oesophageal manifestation of disease compared to the standard tests such as pH monitoring and manometry.

Methods: Patients were recruited into a prospective database of referrals to a tertiary referral center for either resistance to maximal medical therapy or extra-oesophageal symptoms of GORD. Data included 2 channel 24-hour pH monitoring and manometry results, as well as scintigraphic reflux data with late images assessing pulmonary aspiration of refluxate.

Results: Study population included 250 patients (155 F, 95 M) with an average age of 60 years. Patients were clinically classified as either GORD (n=72) or laryngopharyngeal reflux (LPR) (n=178). Pulmonary aspiration of the refluxate was detected significantly more commonly in LPR patients (58/178 compared with GORD 10/72). Strong correlations were found between the scintigraphic time-activity curves in the upper oesophagus and pharynx, and ineffective oesophageal motility and pulmonary aspiration. pH studies correlated with the scintigraphic studies but did not predict aspiration similar to other modalities when evaluated by ROC analysis.

Conclusion: Scintigraphic reflux studies offer a viable alternative test for GORD and extra-oesophageal manifestations of reflux disease. Strong correlations were found between measurable scintigraphic parameters and oesophageal motility and lung aspiration of refluxate. This may provide a more confident decision analysis in patients being considered for fundoplication for troubling extra-oesophageal symptoms.

Keywords: Gastro-esophageal, reflux, scintigraphy, manometry, aspiration, pulmonary

Öz

Amaç: Gastro-özofageal reflü (GÖR) hastalığı %20-40 arası prevalansı ile sık görülen bir sorundur. Bu çalışmada hastalığın özofageal ve özofagus dışı belirtilerini değerlendirmek için sintigrafik bir reflü testinin yararını inceleyerek bunu pH monitorizasyonu ve manometri gibi standart testlerle karşılaştırdık.

Address for Correspondence: Hans Van Der Wall MD, University of Notre Dame, Sydney, Australia
Phone: +61297361040 E-mail: hvanderwall@gmail.com ORCID ID: orcid.org/0000-0003-4184-3330
Received: 14.04.2018 **Accepted:** 17.08.2018

Yöntem: Maksimal medikal tedavi veya GÖR özofagus-dışı belirtiler nedeniyle üçüncü basamak bir referans merkezine yönlendirilmiş hastalar prospektif veri tabanında toplandı. İki kanal 24-saat pH monitorizasyonu ve manometri sonuçları ile reflüksatın pulmoner aspirasyonunu değerlendiren geç görüntülerin dahil edildiği sintigrafik reflü verileri saptandı.

Bulgular: Çalışmaya ortalama 60 yaşında 250 hasta (155 K, 95 E) dahil edildi. Hastalar klinik olarak ya GÖR (n=72) ya da laringofaringeal reflü (LPR) (n=178) olarak ikiye ayrıldı. Reflüksatın pulmoner aspirasyonu LPR hastalarında GÖR hastalarına göre anlamlı olarak daha sık saptandı (58/178'e vs. 10/72). Üst özofagus ile farinkste sintigrafik zaman-aktivite eğrileri arasında ve inefektif özofageal motilite ve pulmoner aspirasyon arasında ciddi korelasyon saptandı. pH testleri sintigrafik incelemelerle uyumlu idi ancak diğer incelemeler gibi ROC analizi ile değerlendirildiğinde sintigrafi de aspirasyonu öngöremedi.

Sonuç: Sintigrafik reflü incelemeleri GÖR ve reflü hastalığının özofagus dışı belirtileri için yararlı bir alternatif testtir. Ölçülebilir sintigrafik parametreler ile özofagus motilitesi ve reflüksatın akciğer aspirasyonu arasında ciddi korelasyon saptanmıştır. Bu inceleme, özofagus dışı semptomu olan ve fundoplikasyon için değerlendirilen hastalarda ilgili karar verme sürecine katkı sağlayabilir.

Anahtar kelimeler: Gastro-özofageal, reflü, sintigrafi, manometri, aspirasyon, pulmoner

Introduction

Gastro-oesophageal reflux disease (GORD) is a common and troubling problem that has a prevalence of 20-40% in its various complex manifestations (1). Variability depends on the criteria utilized in the definition and has now been expanded to "a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications" (Montreal definition, 2006) (2). A problem with the definition is that it encompasses many non-specific symptoms and requires confirmation by endoscopy or the application of a therapeutic trial with a clinical response to confirm the diagnosis. Endoscopy is necessary to confirm the presence of esophagitis and exclude sinister pathology. Even so, endoscopy will miss a high proportion of uncomplicated GORD (>50%) and between 25% and 40% of patients will remain unresponsive or refractory to such clinical trials (3).

These circumstances have led to the requirement for invasive testing such as 24-hour pH monitoring, manometry and impedance reflux measurements. Such testing will fundamentally assess the presence of acidic reflux, lower oesophageal sphincter (LOS) pressures/oesophageal clearance or non-acid reflux, respectively (4). However, the blind spot of these tests is in assessment of the extra-esophageal manifestations of reflux such as cough, recurrent sinusitis, laryngitis or chronic recurrent chest symptoms, particularly in those subgroups who experience silent (or non-heartburn) GORD. Laryngopharyngeal reflux (LPR) and lung aspiration of refluxate are dangerous complications that often occur in the absence of oesophagitis or its primary symptom, heartburn (5). LPR complications have been reported in numerous publications and have been succinctly summarized by Koufman et al (5). These complications include laryngeal carcinoma, vocal cord nodules, laryngospasm and subglottic stenosis.

While there have been a number of scintigraphic reflux studies in the past (6,7,8), there has been no general acceptance of the technique due to the variability in technique and inconsistent results. We have validated (9) and present a simple modification of the existing scintigraphic reflux testing and benchmark the findings against the current reference standards such as 24-hour pH monitoring and manometry. The comparison with impedance will be reported separately. We hypothesized that scintigraphic reflux testing is capable of assessing both the presence of oesophageal disease and its extra-oesophageal manifestations with good correlation with existing testing regimens.

Materials and Methods

Population and Clinical Data

A database of patients with either proven or suspected GORD/LPR [approved by the Institutional Ethics Committee (LNR/12 CRGH/248)] was maintained prospectively. Patients being investigated for suspected GORD/LPR disease with pH/manometry studies was extracted from the database. Patients were chosen for the study if they had mainly upper respiratory tract symptoms that remained undiagnosed after 8 weeks of investigation by appropriate specialists and classified according to the reflux symptom index criteria of Belafsky et al (10). Major upper respiratory tract symptoms documented included cough, sore throat, recurrent throat clearing, voice change, laryngospasm, aspiration, globus and regurgitation. A history of heartburn, regurgitation and dysphagia was routinely elicited. All patients had severe symptoms that were resistant to high-dose proton-pump inhibitor therapy and had been referred for consideration of fundoplication. Scintigraphy was used to prospectively evaluate extra-oesophageal refluxate and the possibility of pulmonary aspiration of refluxate. This is therefore a highly selected group of patients with a strong pre-test probability of GORD causing LPR. A large proportion had a long history of undiagnosed upper respiratory tract symptoms and were studied by scintigraphy in order to evaluate the possibility of reflux disease as a causation. Clinical data was prospectively collected using a standardized proforma and entered into a database.

pH Monitoring (2 Channel)

24-hour impedance reflux study with two channel 24-hour pH was performed on all patients. Following local anesthetic application, a trans-nasal catheter was introduced into the oesophagus. This consisted of 2 level impedance rings and 2 level pH electrodes connected to an external monitoring device and calibrated accordingly. Impedance rings were maneuvered to 5 and 15 cm above the upper border of the LOS (Zephyr device, catheter ZAI-BD31, Sandhill Co, Highlands Ranch, Colorado, USA). No dietary restrictions were made other than ingestion of acidic beverages. Catheter placement was checked by manometry with the lower pH electrode 5 cm above the upper border of the LOS and the upper, 15 mm higher. Patients returned the following day for removal of the assembly. Meal-times were included in the reporting analysis. Reports of 24-hour pH and 24-hour impedance reflux were generated by autoscan and manual review. Reflux was classified according to the consensus on impedance and pH monitoring (11). In summary, this is based on oesophageal pH during reflux detected by impedance monitoring. Acid reflux is defined as a fall in pH below 4, weakly acid reflux as a fall in pH which is ≥4 but <7 and non-acid reflux where oesophageal pH increases ≥7 or remains ≥7 during reflux.

Manometry

Stationary manometry was obtained with a water perfused dent sleeve 8 channel catheter (Dent Sleeve International Mississauga, Ontario, Canada) using standard techniques. Data was recorded with a multichannel recording system (PC polygraph HR Medtronics, Synectics Medical, Minneapolis, Minnesota, United States) and analyzed using the PolyGram software program (Medtronics, Synectics Medical, Minneapolis, Minnesota, United States). Oesophageal motility was graded by the modified method of Kahrilas et al. (11,12). Grades were reported as normal, mildly, moderately or severely ineffective oesophageal motility (IOM). LOS pressure was recorded in all patients.

Scintigraphy

Patients were fasted overnight and medications were ceased for 24 h prior to the test. Patients were positioned upright in front of a Hawkeye 4 gamma camera (General Electric, Milwaukee, United States) with the mandible and stomach in the field of view. They swallowed 40-60 MBq of Tc-99m DTPA diluted in 50 mL of water followed by an additional 50 mL of water to clear activity from the oropharynx and oesophagus.

Dynamic imaging was performed for a duration of 2 minutes at an interval of 15s per frame into a 64*64 matrix. Patients were then placed in a supine position and dynamic images obtained at a framing rate of 30s per frame for 30 minutes. After supine imaging, 40-60 MBq of phytate (colloid) was administered orally with a 50 mL flush of water. Delayed static imaging using a 256*256 matrix was obtained two hours later for assessment of lung aspiration of refluxate. Images were analyzed by regions of interest over the pharynx, upper, mid and lower oesophagus with a background region over the lateral chest. Time-activity curves were generated from each region (Figure 1) Grades was assigned to the time-activity curves as shown in Figure 2. Grade 1 was a declining curve, with grade 2 being flat and grade 3 a rising curve. Delayed images (Figure 3) were analyzed with a line profile for the assessment of aspiration into the main airways (>2 X background).

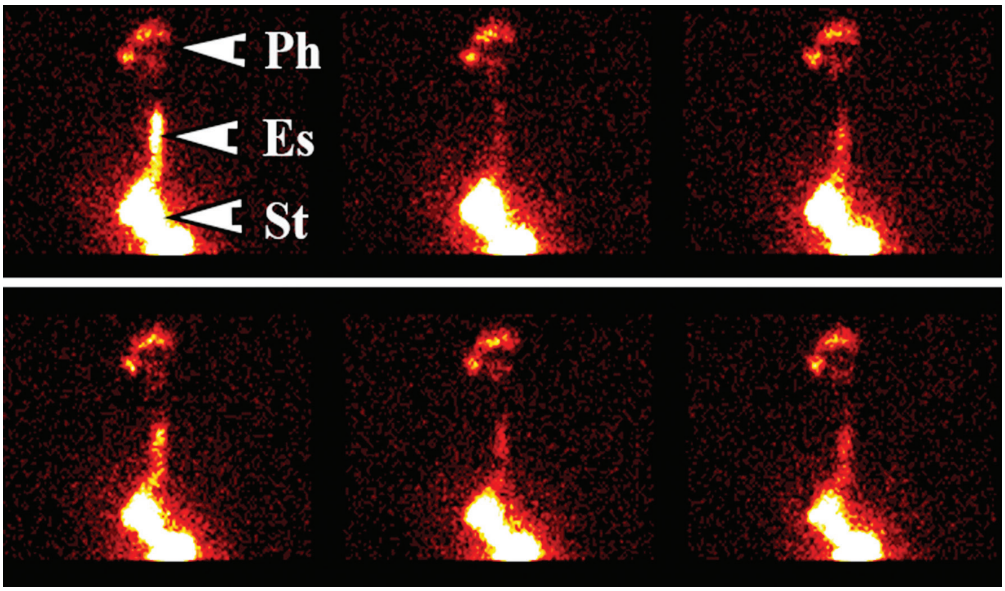


Figure 1. Dynamic sequence of the scintigraphic study showing full-column gastro-oesophageal reflux to the level of the pharynx. The oesophagus and stomach are labelled as Es and St, respectively

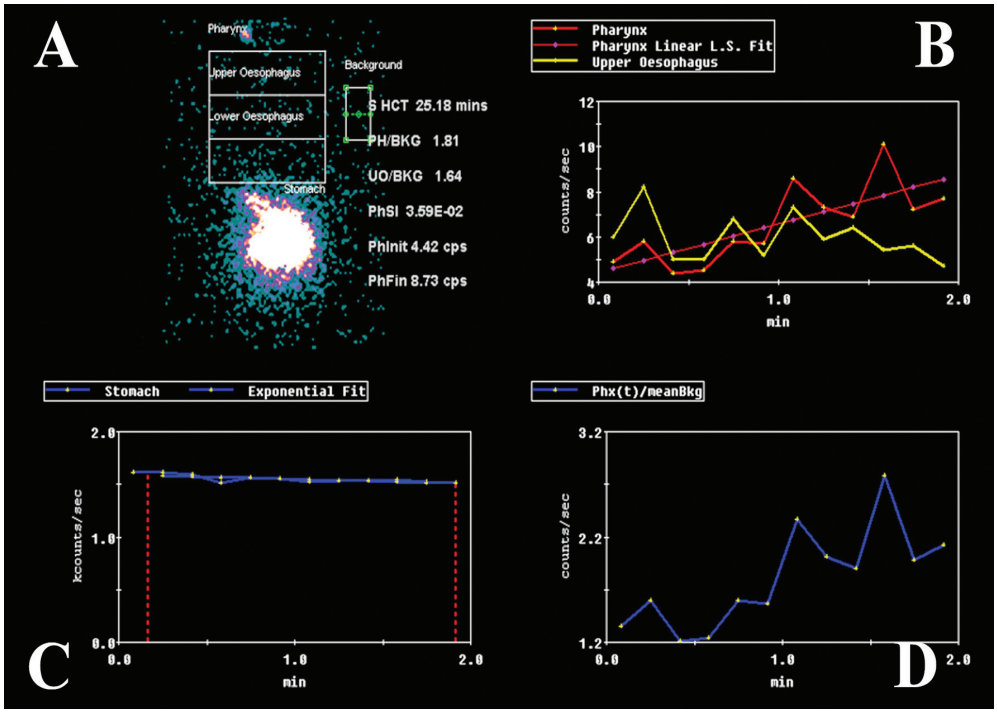


Figure 2. Graphical analysis of the dynamic study. Panel A shows the regions of interest for the pharynx, upper and lower oesophagus and the background regions as well as the relevant results. Panel B shows the time-activity curves for the pharynx (red) with its fitted curve (pink) and the curve for the upper oesophagus (yellow). Panel C is the gastric emptying curve with the time to half clearance being shown at 25.2 minutes in panel A. Panel D indicates the ratio of pharynx to background

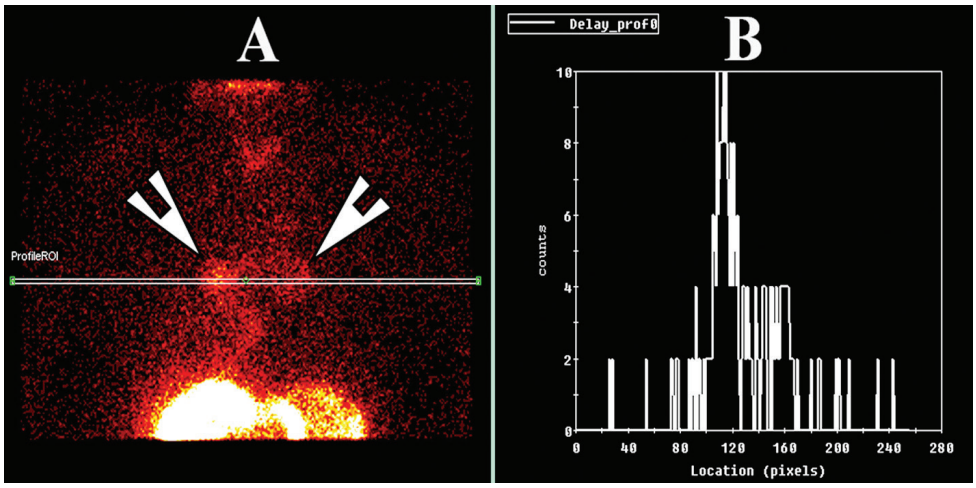


Figure 3. A) The delayed study at 2 hours demonstrates aspiration of tracer into both lungs with significant activity in the main airways (arrowheads). B) The line profile through the hilar regions shows the count densities in the lungs, which is 5 times higher than background activity

Statistical Analysis

Data was analyzed by nonparametric statistical methods as much of the analysis was of ordinal data with multiple studies for each patient. Standard ANOVA statistics, Wilcoxon matched pairs test, Student's t-test and Pearson correlation coefficient (2 tails) with significance levels of 0.05 were utilized. Fisher's exact test (two-tailed) and receiver operating characteristic (ROC) analysis was also undertaken where appropriate. Statistica V8 software (Statsoft, Oklahoma, United States) package was used for data analysis.

Results

Population and clinical data. A total of 250 consecutive patients with complete data were studied (155 F, 95 M) over a period of 24 months. The average age was 60 years with a range of 20-85 years. Clinical history distinguished the patients clinically as predominantly GORD in 72

patients and LPR (±GORD) in 178. All patients underwent 24-hour pH monitoring and water perfused manometry. Scintigraphic studies were acquired within a 3-week period of the standard tests in all patients. A subset of 33 patients underwent laparoscopic fundoplication and these results have been reported elsewhere (9).

Two channel 24-hour pH monitoring. Twenty-four-hour pH studies were normal in 25 patients (pH >4), weakly acidic in 78 (pH >4, <7) and abnormal in the rest (147). Results of the pH findings are shown in Table 1. In patients with scintigraphic evidence of aspiration, 14% (n=10) had normal proximal pH studies while 6% (n=5) had normal distal pH studies.

There was no significant difference in pH studies between patients with LPR and GORD (p>0.05). Moderate correlation was found between proximal and distal acid exposure (Pearson correlation coefficient=0.32, p=0.001).

Proximal and distal acid exposure had no significant correlation with either LOS pressure or oesophageal clearance by manometry (p>0.05). Correlation coefficients were poor (Pearson correlation coefficients ranging from 0.080 to-0.15).

No significant correlation was found between proximal and distal acid exposure and either scintgraphic clearance curves from the pharynx or upper oesophagus (p>0.05).

Manometry: The patients clinically classified as LPR, had severe IOM (35%); compared to the GORD group (17%). This was a significant difference by Fisher's exact test (two-tailed) with p=0.0058. Normal oesophageal motility was found in 27% with LPR symptoms and in 49% with GORD symptoms. This was a significant difference by Fisher's exact test (two-tailed) with p=0.0021.

The mean LOS pressure was 6.3 mmHg [median: 2.3, standard deviation: 8.4 (95% CI: 5.9-7.6) mmHg]. No significant difference was found between the LPR and GORD groups for mean LOS pressure (p>0.01).

Severe IOM was strongly associated with isotope aspiration in both groups [p=0.00 for LPR (Pearson correlation coefficients: 0.54] and p=0.04 for GORD (Pearson correlation coefficients: 0.21).

There was a strong correlation between IOM and rising isotope curves in the pharynx when supine (Pearson correlation coefficients: 0.29, p=0.003) and upright (Pearson correlation coefficients: 0.38, p=0.00).

Table 1. pH study (% acidic reflux/24 hours)

Site	Mean	SD	Range
Proximal upright	6.0	6.8	1.0-34.0
Proximal supine	7.9	6.4	1.0-26.0
Distal upright	5.2	5.2	1.0-26.0
Distal supine	8.5	9.1	1.0-52.0

SD: Standard deviation

Scintigraphy: A total of 68 out of 250 patients demonstrated isotope aspiration into the lungs. There was significantly more pulmonary aspiration of refluxate in the group with LPR (58/178) symptoms than with a GORD profile (10/72) by Fisher's exact test (p=0.0027).

The time activity curves for the pharynx and upper oesophagus with the pulmonary aspiration data for each pattern of curve is shown in Table 2 and 3, respectively. The outstanding feature of these findings is the rarity of isotope aspiration in patients with a declining time activity curve (Grade 1) for the pharynx and upper oesophagus. No patient with a clinical GORD profile had lung aspiration in either the upright or supine position and only 3 of 63 patients with LPR symptoms showed evidence of aspiration. Similar findings were shown for declining time-activity curves for the upper oesophagus. This is in sharp contrast with a rising time activity curve, where a high proportion of patients had evidence of pulmonary aspiration. A declining time-activity curve in the pharynx and upper oesophagus has a negative predictive value (NPV) of 97% for aspiration. Rising curves at both sites have a positive predictive value (PPV) of 98% for aspiration. The results for the pharynx, regardless of the upper oesophageal clearance pattern, were NPV of 98% and PPV of 100%.

The ROC analysis demonstrated that the optimal tests for pulmonary aspiration of refluxate were the scintigraphic time activity curves for the pharynx and upper oesophagus, and the manometric marker of oseophageal clearance (Figure 4). Distal oesophageal total acid exposure and LOS pressures were not significant predictors of lung aspiration

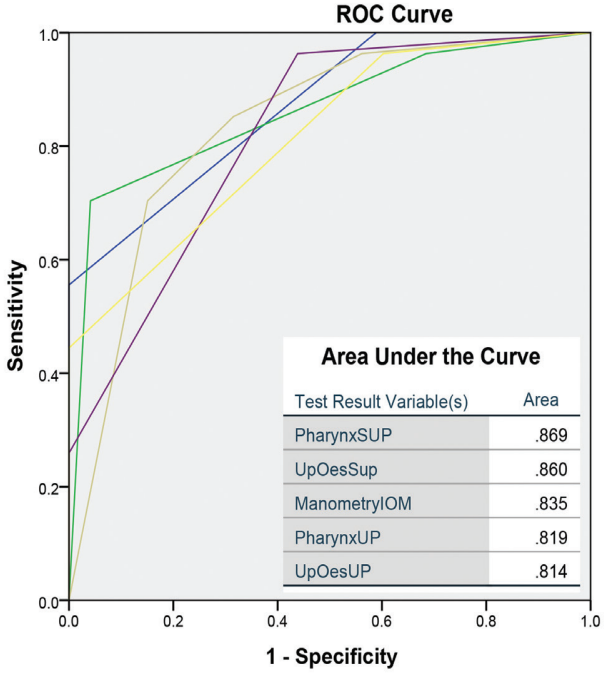


Figure 4. Receiver operating characteristic for the variables as predictors of lung aspiration of refluxate. The area under the curves is inset
ROC: Receiver operating characteristic

Table 2. Pharyngeal time-activity curves for the scintigraphic studies according to symptom profile (laryngopharyngeal reflux versus gastro-oesophageal reflux disease)

Clinical	Grade 1	Aspiration	Grade 2	Aspiration	Grade 3	Aspiration
GORD upright	42	0 (0%)	30	10 (33%)	0	0 (0%)
GORD supine	20	0 (0%)	44	3 (7%)	8	8 (100%)
LPR upright	63	3 (5%)	97	38 (39%)	18	18 (100%)
LPR supine	55	0 (0%)	93	28 (30%)	30	30 (100%)

LPR: Laryngopharyngeal reflux, GORD: Gastro-oesophageal reflux disease

Table 3. Upper oesophageal time-activity curves for the scintigraphic studies according to symptom profile (laryngopharyngeal reflux versus gastro-oesophageal reflux disease)

Clinical	Grade 1	Aspiration	Grade 2	Aspiration	Grade 3	Aspiration
GORD upright	29	3 (10%)	40	5 (13%)	3	3 (100%)
GORD supine	15	0 (0%)	49	5 (10%)	8	5 (63%)
LPR upright	45	0 (0%)	105	30 (29%)	28	28 (100%)
LPR supine	45	3 (7%)	84	13 (15%)	49	43 (90%)

LPR: Laryngopharyngeal reflux, GORD: Gastro-oesophageal reflux disease

(p>0.05) with proximal total acid exposure just reaching significance (p=0.04).

Discussion

This study indicates that scintigraphic reflux studies are a viable alternative to the current suite of testing for the establishment of a diagnosis of GORD. However, the group of patients enrolled in the current study are not a typical representation of how this disease presents in the general community. This is a highly selected group of patients, referred to a tertiary center for resistance to standard therapy or atypical symptoms of GORD. Perhaps the most important finding of this study is that attempting to clinically classify patients as either purely oesophageal disease (GORD) or extra oesophageal disease (LPR) is a futile exercise. A significant proportion of patients classified as GORD will demonstrate pulmonary aspiration of refluxate, which is clinically silent (Figure 3). This has been elegantly shown by similar scintigraphic techniques in 20% of patients with chronic respiratory disease but silent GORD. As little as 0.1 MBq of aspirated activity was detectable in the lungs of these patients (13).

While the scintigraphic reflux study is capable of demonstrating evidence of GORD at the oesophageal level (Figure 1), its other great advantage is the delineation of extra-oesophageal disease. This is clearly reflected at the level of the oropharynx, laryngopharynx and the lungs. These areas are not screened by the existing suite of testing such as manometry and pH and with some reservations by impedance monitoring. Refluxate contaminating the extra-oesophageal tissues can be visualized and although 27% of patients showed evidence of pulmonary aspiration of refluxate, this may in fact be an underestimate of the true incidence of pulmonary aspiration in this type of patient cohort. Patients are supine for approximately 30 minutes and are essentially upright for the other 90 minutes prior to the delayed scan for pulmonary aspiration. This may in fact be significantly worse when the patient is supine and asleep at night (14).

Analysis of the scintigraphic time-activity curves for the pharynx and upper oesophagus showed a strong correlation with IOM, indicating that inability to adequately clear refluxate from the oesophagus is of significant importance in addition to the incompetence of the LOS tone in both GORD and LPR patients with pulmonary aspiration of refluxate. LOS tone was not a good discriminator as the majority of referred patients had poor tone with a mean of 6.3 mmHg (N~26 mmHg) (15). When analyzing the ROC curves, IOM was as useful as the scintigraphic time-activity curves in predicting aspiration of refluxate (Figure 4). This observation confirms that the scintigraphic technique is also useful in detecting dysmotility, as the time-activity curves will accurately reflect this. A rising curve is the end result of recurrent episodes of reflux and the inability of the oesophageal clearance mechanisms to remove the refluxate. Dysmotility is a key marker for LPR as has been shown by others, particularly in those with silent reflux and extra-oesophageal symptoms such as cough (16,17).

Earlier studies with 24-hour ambulatory pH monitoring have pointed out the importance of distal rather than proximal oesophageal pH as being important in patients with heart-burn and respiratory complications of GORD (18). Others have attempted to rationalize the disparity by suggesting that acid is neutralized during the ascent to the proximal oesophagus and may not register on the proximal pH probe (19). It is our contention that distal oesophageal pH does not fully emulate what is happening in the upper

oesophagus and pharynx which is essentially beyond the level of the pH probe and therefore, is fundamentally a blind spot. This verifies the hypothesis of a poor correlation between pH studies in the distal oesophagus and lung aspiration of isotope to be true. The ROC analysis shows a poor performance for total distal acid exposure [Area under the curve (AUC)=0.597, p=0.179] and a marginally better and barely significant finding with total proximal acid exposure (AUC=0.651, p=0.036) in patients with aspiration of refluxate. The scintigraphic variables and IOM were comparatively better performers in the prediction of pulmonary aspiration of refluxate (AUC~0.850).

It must however be acknowledged that the published data which validates 24-hour pH monitoring is fundamentally concerned with the typical symptoms of heartburn and acid regurgitation. This imposes a significant limitation and may subsequently lead to an under diagnosis, particularly in the group of patients with silent reflux. In this group of patients, pH testing may not be the optimal choice of test for diagnosis of the disease. Some theories suggest that neutral or basic pH is equally or more significant than acidic pH. Refluxate may contain pepsin and bile contents that have also been implicated in tissue injury in the laryngopharynx (20,21). The data presented here illustrates the poor correlation between positive distal pH and pulmonary aspiration (3). Some studies have demonstrated pepsin in the laryngeal epithelium after a reflux event and questions have been raised as to the potential damage which may be caused (20,21). Failure to identify this group of patients could subsequently lead to progression of the disease and the development of secondary manifestations (22,23) such as laryngeal carcinoma, vocal cord granulomas and pulmonary aspiration and its multiplicity of complications such as bronchiectasis, lung fibrosis etc. The major diagnostic issue is attempting to imply the presence of refluxate through indirect markers of pH monitoring and manometry. Scintigraphic studies allow direct visualization of activity in the laryngopharynx and lungs. Importance of the diagnostic algorithm for LPR versus GORD is that LPR requires more stringent medical therapy, which has a high failure rate and leads to earlier contemplation of fundoplication, particularly if there is lung aspiration of refluxate (5).

The negative and positive predictive values of the scintigraphic time-activity curves for the oesophagus and pharynx as predictors of pulmonary aspiration were very good at 97% and 98%, respectively. This was an unexpected finding and may prove to be of clinical value in patients with a high clinical suspicion of aspiration, but no scan evidence in the delayed study. It may inform the decision to undertake fundoplication for severe cases of reflux with a strong clinical suspicion of aspiration. It is also reassuring to physically see GORD in the dynamic studies and then refluxate in the lungs in the delayed phase of the study, particularly in silent (heartburn negative) disease with manifest extra-oesophageal symptoms such as cough, globus etc.

The principal weakness of this study is the highly selected cohort of patients who already had a high pre-test probability of disease. It requires assessment in general community patients to ascertain its false positive rate. To this end, we have commenced a study in normal subjects with acquisition of reflux studies in 25 asymptomatic volunteers. Preliminary findings in 10 cases demonstrates low-grade gastroesophageal reflux in three and then to the mid-esophagous when in the upright position only. The others showed no evidence of reflux.

Conclusion

We describe an innovative nuclear scintigraphic reflux test and its performance on a cohort of patients referred to a tertiary referral center for failure to respond to therapy of typical or atypical symptoms. This test has the potential to re-define the current understanding of GORD as it considers the broad definition of GORD. A strong correlation was found between scintigraphic parameters in the pharynx and upper oesophagus, and markers of ineffective oesophageal clearance consistent with dysmotility. These parameters were strongly predictive of pulmonary aspiration of the refluxate. pH studies were weakly correlated with these parameters and of little use in predicting laryngeal exposure and pulmonary aspiration.

Ethics

Ethics Committee Approval: Concord Hospital Institutional Ethics Committee (LNR/12 CRGH/248).

Informed Consent: Obtained in writing from all patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.L.F., S.P., Concept: L.B., G.L.F., Design: G.L.F., H.V.D.W., Data Collection or Processing: L.B., H.V.D.W., M.C., Analysis or Interpretation: L.B., G.L.F., H.V.D.W., Literature Search: L.B., S.P., Writing: L.B., H.V.D.W., G.L.F., S.P., M.C.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: No funding was received for the project.

References

1. Spechler SJ. Epidemiology and natural history of gastro-oesophageal reflux disease. Digestion 1992;51(Suppl 1):24-29.
2. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R; Global Consensus Group. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 2006;101:1900-1920.
3. Richter JE. How to manage refractory GERD. Nat Clin Pract Gastroenterol Hepatol 2007;4:658-664.

4. De Giorgi F, Palmiero M, Esposito I, Mosca F, Cuomo R. Pathophysiology of gastro-oesophageal reflux disease. Acta Otorhinolaryngol Ital 2006;26:241-246.
5. Koufman J, Aviv JE, Casiano RR, Shaw GY. Laryngopharyngeal Reflux: Position Statement of the Committee on Speech, Voice, and Swallowing Disorders of the American Academy of Otolaryngology-Head and Neck Surgery. Otolaryngol Head Neck Surg 2002;127:32-35.
6. Caglar M, Volkan B, Alpar R. Reliability of radionuclide gastroesophageal reflux studies using visual and time-activity curve analysis: inter-observer and intra-observer variation and description of minimum detectable reflux. Nucl Med Commun 2003;24:421-428.
7. Kjellen G, Brudin L, Hakansson HO. Is scintigraphy of value in the diagnosis of gastrooesophageal reflux disease? Scand J Gastroenterol 1991;26:425-430.
8. Shay SS, Abreu SH, Tsuchida A. Scintigraphy in gastroesophageal reflux disease: a comparison to endoscopy, LESp, and 24-h pH score, as well as to simultaneous pH monitoring. Am J Gastroenterol 1992;87:1094-1101.
9. Falk GL, Beattie J, Ing A, Falk SE, Magee M, Burton L, Van der Wall H. Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? World J Gastroenterol 2015;21:3619-3627.
10. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice 2002;16:274-277.
11. Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A. Esophageal peristaltic dysfunction in peptic esophagitis. Gastroenterology 1986;91:897-904.
12. Kahrilas PJ, Dent J, Dodds WJ, Hogan WJ, Arndorfer RC. A method for continuous monitoring of upper esophageal sphincter pressure. Dig Dis Sci 1987;32:121-128.
13. Ruth M, Carlsson S, Mansson I, Bengtsson U, Sandberg N. Scintigraphic detection of gastro-pulmonary aspiration in patients with respiratory disorders. Clin Physiol 1993;13:19-33.
14. Barish CF, Wu WC, Castell DO. Respiratory complications of gastroesophageal reflux. Arch Intern Med 1985;145:1882-1888.
15. Richter JE, Wu WC, Johns DN, Blackwell JN, Nelson JL, Castell DO. Esophageal manometry in 95 healthy adult volunteers. Variability of pressures with age and frequency of "abnormal" contractions. Dig Dis Sci 1987;32:583-592.
16. Agreus L. The epidemiology of functional gastrointestinal disorders. Eur J Surg(Suppl)1998:60-66.
17. Kastelik JA, Redington AE, Aziz I, Buckton GK, Smith CM, Dakkak M, Morice AH. Abnormal oesophageal motility in patients with chronic cough. Thorax 2003;58:699-702.
18. Gastal OL, Castell JA, Castell DO. Frequency and site of gastroesophageal reflux in patients with chest symptoms. Studies using proximal and distal pH monitoring. Chest 1994;106:1793-1796.
19. Charbel S, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients on PPI therapy. Am J Gastroenterol 2005;100:283-289.
20. Gill G, Johnston N, Buda A, Pignatelli M, Pearson J, Dettmar PW, Koufman J. Laryngeal epithelial defenses against laryngopharyngeal reflux: investigations of E-cadherin, carbonic anhydrase isoenzyme III, and pepsin. Ann Otol Rhinol Laryngol 2005;114:913-921.
21. Johnston N, Knight J, Dettmar PW, Lively MO, Koufman J. Pepsin and carbonic anhydrase isoenzyme III as diagnostic markers for laryngopharyngeal reflux disease. Laryngoscope 2004;114:2129-2134.
22. Khan AM, Hashmi SR, Elahi F, Tariq M, Ingrams DR. Laryngopharyngeal reflux: A literature review. Surgeon 2006;4:221-225.
23. Rathod NR. Extra-oesophageal presentation of gastro-oesophageal reflux disease. J Indian Med Assoc 2010;108:18-20.

Lung
https://doi.org/10.1007/s00408-018-0128-4

PULMONARY ASPIRATION

Gastro-Oesophageal Reflux and Aspiration: Does Laparoscopic Fundoplication Significantly Decrease Pulmonary Aspiration?

Oleksandr Khoma[1,6] · Susanna Elizabeth Falk[2] · Leticia Burton[3] · Hans Van der Wall[3] · Gregory Leighton Falk[3,4,5]

Received: 28 February 2018 / Accepted: 23 May 2018

Abstract

Purpose Pulmonary aspiration of gastric refluxate is one of the indications for anti-reflux surgery. Effectiveness of surgery in preventing pulmonary aspiration post-operatively has not been previously tested. The aim of this project is to assess effectiveness of anti-reflux surgery on preventing pulmonary aspiration of gastric refluxate.

Methods Retrospective analysis of prospectively populated database of patients with confirmed aspiration of gastric refluxate on scintigraphy. Patients that have undergone anti-reflux surgery between 01/01/2014 and 31/12/2015 and had scintigraphy post-operatively were included. Objective data such as resolution of aspiration, degree of proximal aero-digestive contamination, surgical complications and oesophageal dysmotility as well as patient quality of life data were analysed.

Results Inclusion criteria were satisfied by 39 patients (11 male and 28 female). Pulmonary aspiration was prevented in 24 out of 39 patients (61.5%) post-operatively. Significant reduction of isotope contamination of upper oesophagus supine and upright ($p=0.002$) and pharynx supine and upright ($p=0.027$) was confirmed on scintigraphy post-operatively. Severe oesophageal dysmotility was strongly associated with continued aspiration post-operatively OR 15.3 (95% CI 2.459–95.194; $p=0.02$). Majority (24/31, 77%) of patients were satisfied or very satisfied with surgery, whilst 7/31 (23%) were dissatisfied. Pre-operative GIQLI scores were low (mean 89.77, SD 20.5), modest improvements at 6 months (mean 98.4, SD 21.97) and deterioration at 12 months (mean 88.41, SD 28.07) were not significant ($p=0.07$).

Conclusion Surgery is partially effective in reversing pulmonary aspiration of gastric refluxate on short-term follow-up. Severe oesophageal dysmotility is a predictor of inferior control of aspiration with surgery.

Keywords LPR · GORD · Pulmonary aspiration · Laparoscopic fundoplication · Scintigraphy

Introduction

Pulmonary aspiration of gastric refluxate is a feared complication of gastro-oesophageal reflux disease (GORD). Patients presenting with typical symptoms of GORD and those with symptoms of extraoesophageal reflux are at risk of pulmonary aspiration [1–3]. Scintigraphy is currently the only available test to objectively demonstrate pulmonary aspiration in GORD [2].

Recurrent pulmonary aspiration can result in significant symptoms and cause permanent damage to the lungs (bronchiectasis, recurrent infections, adult onset asthma, pulmonary fibrosis and lung transplant rejection) and laryngeal disease (voice changes, laryngeal stenosis and laryngeal cancer) [3–6]. Laparoscopic anti-reflux surgery (LARS) is a common treatment offered to patients failing medical therapy for GORD [7, 8]. The effectiveness of laparoscopic fundoplication in reducing pulmonary aspiration post-operatively has

✉ Oleksandr Khoma
khoma.a@gmail.com

1 Department of Upper Gastro-Intestinal Surgery, Concord Repatriation General Hospital, Hospital Road, Concord, NSW 2137, Australia

2 Sydney Heartburn Clinic, 29/12-18 Tryon Road, Lindfield, NSW 2070, Australia

3 Concord Nuclear Imaging, Suite 101/5 Bay Dr, Meadowbank, NSW 2114, Australia

4 Concord Repatriation General Hospital, Sydney, Australia

5 University of Sydney, 29/12-18 Tryon Road, Lindfield, NSW 2070, Australia

6 Lindfield, Australia

Published online: 26 May 2018

not been previously tested, although anecdotally utilised for many years [9].

Patients and Methods

A single surgeon prospective cohort study of consecutive patients with a positive pre-operative pulmonary aspiration scan and undergoing 360-degree laparoscopic fundoplication for severe reflux disease is reported. Patient data were acquired between 01/01/2014 and 31/12/2015.

The data were extracted from a prospectively populated database that was approved by the Concord Hospital Ethics Committee (LNR/12 CRGH/248). Inclusion criteria were pulmonary aspiration on pre-operative scintigraphy and follow-up post-operative scintigraphy. Exclusion criteria were failure to attend post-operative scintigraphy, technically inadequate pre-operative scan and loss to follow-up.

All patients were pre-operatively interviewed by an experienced senior upper gastro-intestinal surgeon and were diagnosed as having predominantly gastro-oesophageal (GOR) or predominantly laryngopharyngeal (LPR) symptoms. Patients with massive hiatal hernia (> 30% of stomach above diaphragm) were identified as a separate subgroup (MHH). Patient selection was planned to include dual-channel 24-pH monitoring, multi-channel oesophageal impedance, oesophageal manometry and gastroscopy. Patients were asked to complete gastro-intestinal quality of life index questionnaire (GIQLI), Respiratory Symptoms Index (RSI) before the operation and then at 3, 6, 12 and 24 months after surgery [10, 11].

Patients with ongoing pulmonary symptoms despite maximum medical therapy and evidence of pulmonary aspiration on scintigraphy and symptoms or objective evidence of pulmonary disease were offered surgery. Patients were also operated for typical GORD symptoms.

All operations were 360-degree composite fundoplication with repair of the hiatal pillars. Detailed operative technique was previously described by one of the authors [12].

Reflux aspiration scintigraphy was conducted using validated technique [13]. Scintigraphy was performed after an overnight fast using Hawkeye 4 gamma camera (General Electric, Milwaukee, United States) with stomach, chest and upper airway in the field of view. 40–60 MBq of 99mTc DTPA was administered orally mixed with 150–200 ml of water. Images were obtained for 5 min at 15 s per frame into a 64 × 64 matrix, followed by a 30-min dynamic image whilst supine for 30 s per frame. Aspiration was proven on delayed images at 2 h by the presence of isotope in the lungs (Fig. 1). Isotope time-activity curves (Fig. 2) were recorded for pharynx and upper oesophagus supine and erect and classified as showing no reflux, falling, flat or rising curves (0–3).

Statistical analysis was performed using SPSS Statistics 23 software (IBM, New York, United States). Standard ANOVA statistics, student's *t* test, Fisher's exact test, χ^2 test and Pearson correlation coefficient (2 tails) were used. Result with *p* value of 0.05 or less were considered significant.

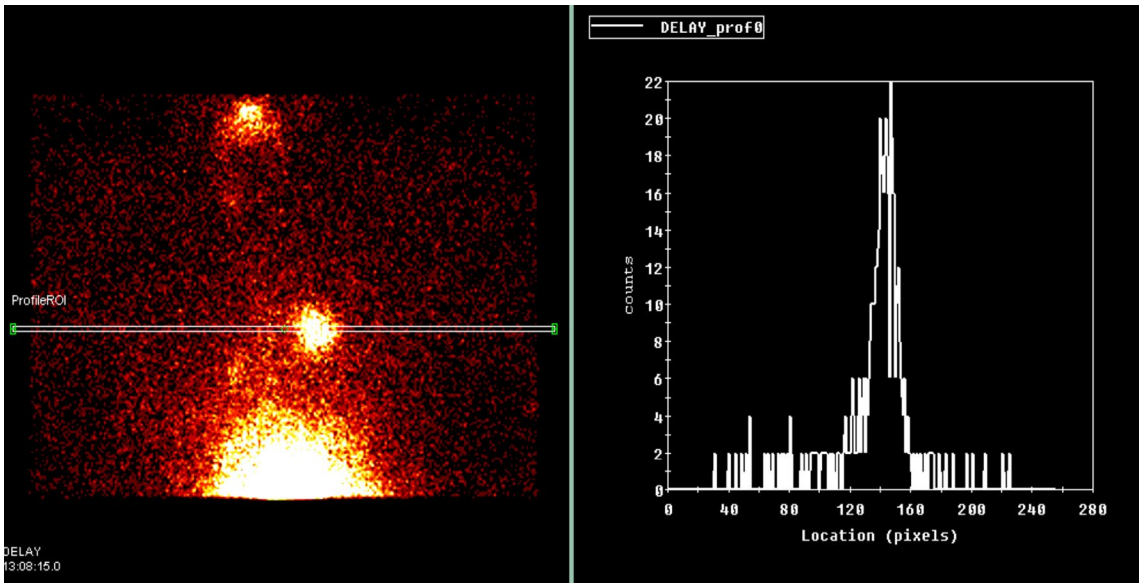


Fig. 1 Delayed study showing aspiration of tracer into left lung and the line profile showing the count profiles through this region. A high-count profile is apparent for the left lung activity

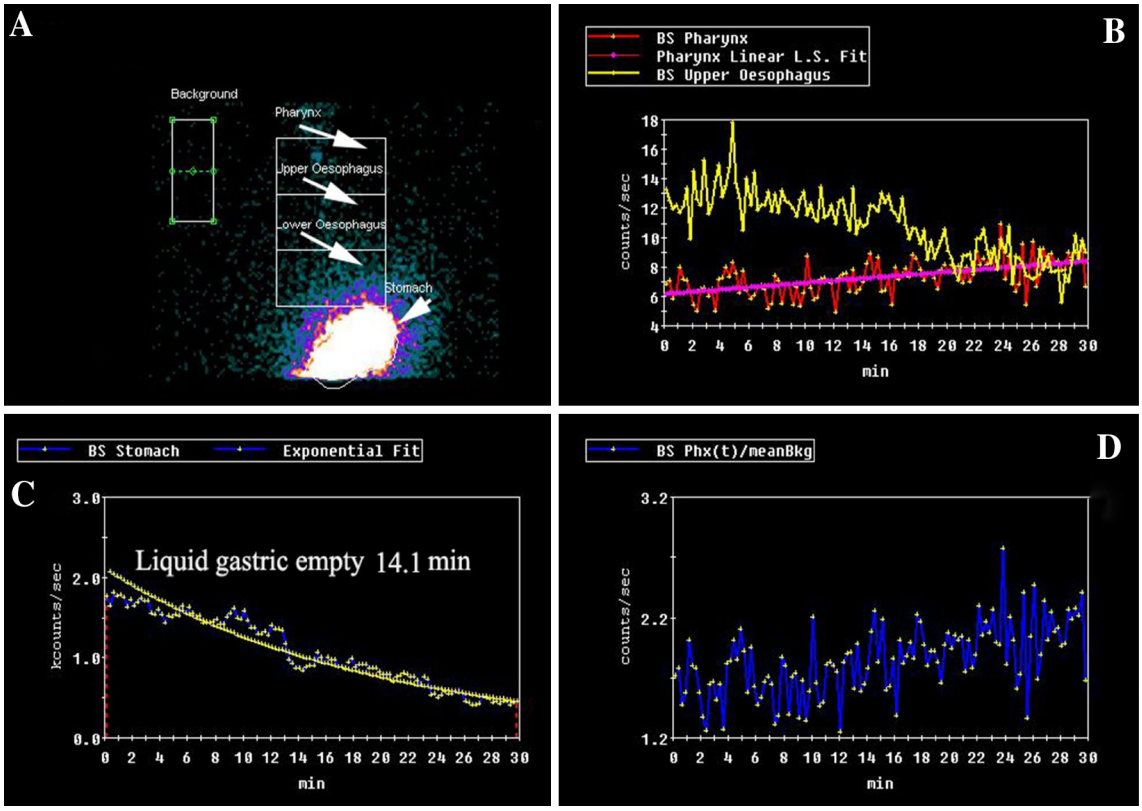


Fig. 2 Typical graphical analysis of the scintigraphic study showing the regions of interest for the pharynx, oesophagus, stomach and background in the top left panel (**a**). Time-activity curves are generated for the pharynx and upper oesophagus, with an exponential fit to the curve for the stomach (**c**). The time to half clearance for liquid contents is determined from this curve (14.1 min). **b** Analysis of the time-activity curves for the pharynx (red curve) with the curve of best fit to the data points (pink curve). The curve for the upper oesophagus is shown in yellow. A rising curve is apparent for the pharynx. **d** Graphical representation of the ratio of pharyngeal to background time-activity curves. This is used for quality assurance and gives an idea of the amplitude of the reflux relative to background

Results

Inclusion criteria were satisfied by 39 patients (11 male and 28 female). Indications for surgery were as follows: massive hiatal hernia (6 patients), predominantly LPR (21 patients) and predominantly GOR (12 patients). Patients had pre- and post-operative scintigraphy aspiration scans within 12 months of surgery. Pre-operative manometry was performed on 33 patients. Quality of life data were available for 26 patients pre-operatively, 18 patients at 6 months and 22 patients at 12 months (Table 1).

All patients had evidence of reflux on pre-operative scintigraphy, including 32 patients with intermittent reflux, five with continuous reflux and two patients with evidence of reflux that was ungraded. Post-operatively, there was no evidence of reflux in four patients, intermittent reflux in 32 and continuous reflux in three patients.

Oesophageal motility was classified using modified classification based on Kahrilas et al. [14]. Patients with 2–3 out of 10 ineffective swallows were labelled as having "mild", 4–5 out of 10 as "moderate" and 6 or more ineffective swallows as "severe" oesophageal dysmotility [14]. Motility was normal in six patients (18.2%), seven patients (21.2%) had mild category, six (18.2%) patients had moderate and 14 (42.4%) patients had severe ineffective oesophageal motility (IOM). Pulmonary aspiration in this group was strongly associated with severe IOM (χ^2, $p = 0.001$).

Pulmonary aspiration was prevented in 24 out of 39 patients (61.5%) post-operatively as determined by

Table 1 Patients characteristics

Age, years	60.2 (range 31–78)
Gender	Male = 11; female = 28
Symptom profile	
LPR	21
GORD	12
MHH	6
Oesophageal motility	
Normal	18.20%
Mild IOM	21.20%
Moderate IOM	18.20%
Severe IOM	42.40%

scintigraphy. Aspiration was best controlled in patients without severe grade oesophageal dysmotility (89.5% resolution of aspiration). Confirmed aspiration was seen in 9 patients (64.3%) with severe oesophageal dysmotility post-operatively (Table 2). Severe oesophageal dysmotility was strongly associated with continued aspiration post-operatively OR 15.3 (95% CI 2.459–95.194; $p=0.02$) (Chart 3).

Analysis of pharyngeal and upper oesophageal isotope curves revealed significant reduction of isotope contamination of upper oesophagus supine and upright ($p=0.002$) and pharynx supine and upright ($p=0.027$) post-operatively.

Scores of overall satisfaction with surgery scores were available for 31 patients. Majority (24/31, 77%) of patients were satisfied or very satisfied with surgery, whilst 7/31 (23%) were dissatisfied. Satisfaction scores were independent of scintigraphy of post-operative aspiration or severe oesophageal dysmotility. Most common post-operative complaints were of dysphagia ($n=8$), mild epigastric or chest pain ($n=4$) and bloating ($n=4$). Endoscopic dilatation was required in four patients to manage post-operative dysphagia.

Quality of life was impaired in most patients which was reflected in pre-operative GIQLI scores (mean 89.77, SD 20.5). Modest improvements at 6 months (mean 98.4, SD 21.97) and deterioration at 12 months (mean 88.41, SD 28.07) were not significant ($p=0.07$). (Table 3).

Discussion

Reflux pulmonary aspiration may cause symptoms and occasionally serious complications. It is uncommon in the general population, however, prevalence in a highly selected group of patients referred for specialist surgical opinion following failure of maximum medical therapy can be as high as 24% [15]. Potential long-term consequences of pulmonary aspiration and pharyngeal contamination by refluxate include bronchiectasis, adult onset asthma, recurrent pneumonia, laryngeal stenosis, voice changes and laryngeal cancer and possibly "idiopathic" pulmonary fibrosis [6, 9, 16].

Evidence of the effectiveness of treatment of extraoesophageal reflux symptomatology is weak [17, 18]. Multiple

Table 2 Resolution of pulmonary aspiration post-operatively in various IOM groups

	Normal motility	Mild IOM	Moderate IOM	Severe IOM
Post-operative aspiration	0/6	1/7	1/6	9/14
% ongoing aspiration	0%	14.3%	16.7%	64.3%

Chart 3 Association between severe IOM and post-operative aspiration

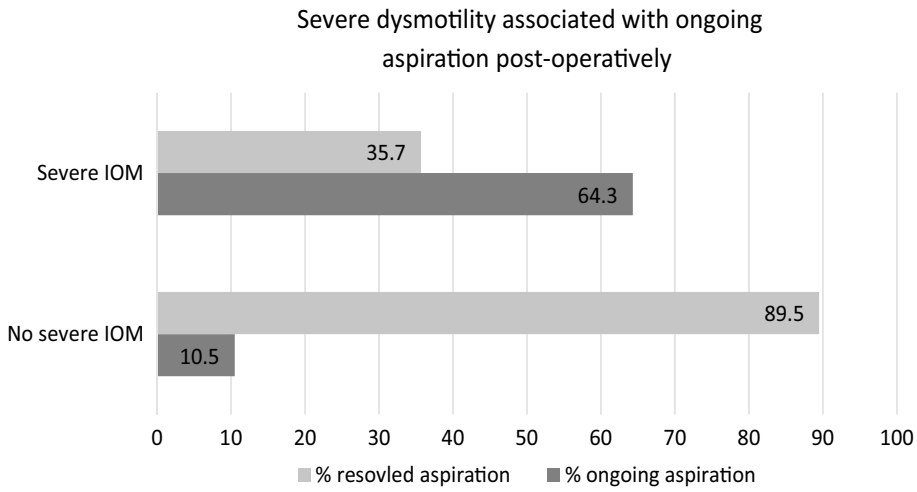


Table 3 Quality of life

Score	Pre-op ($n=26$)	6 months ($n=18$)	12 months ($n=22$)
GIQOL	89.77 (48–117; SD 20.05)	98.4 (43–133; SD 21.97)	88.41 (34–132; SD 28.07)
Visik	3.12 (1–4; SD 1.01)	2.06 (1–4; SD 0.83)	3.05 (2–4; SD 0.97)
Dysphagia	34.14 (15–45; SD 7.74)	33.61 (2.5–45; SD 10.82)	30.57 (5–45; SD 11.67)
Demester	8.42 (0–13; SD 3.2)	7.39 (2–13; SD 3.35)	7.82 (2–12; SD 3)
LPR	22.85 (0–45; SD 13.6)	17.44 (4–43; SD 11.44)	22.27 (1–44; SD 14.34)

studies have evaluated safety and effectiveness of surgical management of severe reflux without specific focus on patients with respiratory symptoms. Although some controversy still exists [19], it is generally accepted that LARS can be offered to patients with reflux disease who have failed medical therapy [7–9, 17].

Proton-pump inhibitors (PPI) are only effective in reducing the acidity of gastric contents and only have minor effect on volume and frequency of reflux as well as reflux of other gastric and pancreatic enzymes and bile that are commonly found in stomach [20, 21]. Association between PPI and community-acquired pneumonia has been previously established [22]. Furthermore, new data from a large US study suggest link between long-term PPI use and significantly increased mortality [23]. Therefore, reducing the amount, frequency and proximal extent of reflux as well as preventing pulmonary aspiration should be goals of treatment in patients with GOR and LPR.

The Society of American Gastrointestinal and Endoscopic Surgeons lists pulmonary aspiration as one of the indications for anti-reflux surgery [24]. Proximal oesophageal acid reflux on 24-h pH monitoring has been associated with pulmonary aspiration, however, this test is limited by inability to detect non-acidic reflux episodes and does not positively diagnose pulmonary aspiration being merely an indicator of probability [15]. Oesophageal impedance has an advantage of detecting non-acid reflux episodes; however, results in the proximal oesophagus are commonly difficult to interpret and clinical relevance of the test has been questioned by some authors [25]. Scintigraphy is currently the only test available to objectively demonstrate pulmonary aspiration [13, 15].

This is the first study demonstrating relative effectiveness of LARS in objective relief of pulmonary aspiration. Significant reduction in pharyngeal and upper oesophageal contamination with refluxate post-operatively further supports the potential benefit of surgery in patients with severe reflux. This reduction in pharyngeal contamination suggests a reduction in pulmonary aspiration severity, which may reduce pulmonary symptoms or damage.

Durability of surgical control of aspiration and symptoms remains unknown. This study focuses on short-term follow-up results. Patient satisfaction and symptom control after LARS for GORD have been previously reported to be sustained at 10 years [26]. Future studies looking at long-term outcomes of surgery in the subgroup of patients with severe reflux with pulmonary aspiration are necessary.

It has been previously established that IOM is associated with increased risk of aspiration in patients with LPR and GOR [15]. This study indicates that severe IOM also predicts worse outcomes of LARS in patients with pulmonary aspiration. Close to 90% of aspiration was relieved in patients with normal motility and mild or moderate IOM, whilst a substantial 64% of patients with severe IOM continued to aspirate to a lesser extent after surgery. Furthermore, in patients with severe IOM curves of pharyngeal and upper oesophageal contamination on scintigraphy did not improve post-operatively. Considering that patient satisfaction with the proposed treatment is determined by their expectations of the treatment effect, it is relevant to identify patients with less favourable prognosis. The presence of severe IOM increases risk of ongoing aspiration despite surgery by at least 2.5-fold (95% CI 2.459–95.194; $p = 0.02$). Although many of the patients with ongoing aspiration reported improvement in symptoms after surgery scintigraphy was not predictive. Longer duration studies are required to demonstrate prevention of lung and laryngeal damage.

In patients with massive hiatal hernia, four out of six continued to aspirate post-operatively (66%). This was of no valid statistical assessment due to tiny sample size of the subgroup; however, a more focused study of reversal of aspiration in patients with giant hiatal hernia are warranted and underway.

Quality of life scores were low in this group of patients. Although modest improvement in QoL scores was observed at six and deterioration at 12 months, it is remarkable that mean score remained low and none of the patient's quality of life scores were comparable with healthy subjects. Lack of significant improvement in GIQLI scores may be attributed to a small sample size. GIQLI also may not be an optimal tool for this group of patients as it will neglect improvement in respiratory symptoms whilst being negatively affected by post-operative dysphagia which is a known side-effect of laparoscopic fundoplication [27]. Relevant quality of life tool that includes respiratory and laryngeal symptoms in addition to the gastro-intestinal symptoms is warranted to assess the effect of surgery on other systems affected by extraoesophageal reflux. Leicester cough questionnaire is one of the validated tools that may be more appropriate to reflect an effect of surgery on quality of life of patients with predominant respiratory complications of reflux disease [28].

This study was limited by being a cohort design, having a small sample size and short follow-up period.

Conclusion

Laparoscopic fundoplication may partially alleviate pulmonary aspiration and pharyngeal contamination in patients with severe, treatment-resistant proximal gastro-oesophageal reflux disease.

Oesophageal dysmotility is one of the key risk factors for aspiration in GOR and LPR. Severe IOM is associated with higher risk of persistent aspiration after surgery.

Long-term effect of surgical treatment of pulmonary aspiration on respiratory and laryngeal function is not known.

Compliance with Ethical Standards

Conflict of interest All authors declare no conflict of interest.

References

1. Barry DW, Vaezi MF (2010) Laryngopharyngeal reflux: more questions than answers. Clevel Clin J Med 77(5):327–334. https://doi.org/10.3949/ccjm.77a.09121
2. Falk GL, Beattie J, Ing A, Falk SE, Magee M, Burton L, Van der Wall H (2015) Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? World J Gastroenterol 21(12):3619–3627. https://doi.org/10.3748/wjg.v21.i12.3619
3. Postma GN, Halum SL (2006) Laryngeal and pharyngeal complications of gastroesophageal reflux disease. GI Motil Online. https://doi.org/10.1038/gimo46
4. Koufman JA, Aviv JE, Casiano RR, Shaw GY (2002) Laryngopharyngeal reflux: position statement of the committee on speech, voice, and swallowing disorders of the American Academy of Otolaryngology-Head and Neck Surgery. Otolaryngology 127(1):32–35
5. Blondeau K, Mertens V, Vanaudenaerde BA, Verleden GM, Van Raemdonck DE, Sifrim D, Dupont LJ (2008) Gastro-oesophageal reflux and gastric aspiration in lung transplant patients with or without chronic rejection. Eur Respir J 31(4):707–713. https://doi.org/10.1183/09031936.00064807
6. Lee JS, Collard HR, Raghu G, Sweet MP, Hays SR, Campos GM, Golden JA, King TE (2010) Does chronic microaspiration cause idiopathic pulmonary fibrosis? Am J Med 123(4):304–311. https://doi.org/10.1016/j.amjmed.2009.07.033
7. Vaezi MF (2009) Extraesophageal Reflux. Plural Publishing, San Diego
8. Luketich JD (2014) Master techniques in surgery: esophageal surgery. Wolters Kluwer Health, Philadelphia
9. Martinucci I, de Bortoli N, Savarino E, Nacci A, Romeo SO, Bellini M, Savarino V, Fattori B, Marchi S (2013) Optimal treatment of laryngopharyngeal reflux disease. Ther Adv Chronic Dis 4(6):287–301. https://doi.org/10.1177/2040622313503485
10. Eypasch E, Williams JI, Wood-Dauphinee S, Ure BM, Schmulling C, Neugebauer E, Troidl H (1995) Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. Br J Surg 82(2):216–222
11. Belafsky PC, Postma GN, Koufman JA (2001) The validity and reliability of the reflux finding score (RFS). Laryngoscope 111(8):1313–1317. https://doi.org/10.1097/00005537-200108000-00001
12. Gibson SC, Wong SK, Dixon AC, Falk GL (2013) Laparoscopic repair of giant hiatus hernia: prosthesis is not required for successful outcome. Surg Endosc 27(2):618–623. https://doi.org/10.1007/s00464-012-2501-3
13. Falk M, Van der Wall H, Falk GL (2015) Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms. Nucl Med Commun 36(6):625–630. https://doi.org/10.1097/mnm.0000000000000289
14. Kahrilas PJ, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A (1986) Esophageal peristaltic dysfunction in peptic esophagitis. Gastroenterology 91(4):897–904
15. Khoma O, Burton L, VanderWall H, Falk M, Falk GL (2017) Pathophysiology of laryngopharyngeal reflux disease: association with pulmonary aspiration on scintigraphy and abnormal oesophageal motility disease (**under review**)
16. McShane PJ, Naureckas ET, Tino G, Strek ME (2013) Non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 188(6):647–656. https://doi.org/10.1164/rccm.201303-0411CI
17. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R (2006) The montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol 101(8):1900–1920. https://doi.org/10.1111/j.1572-0241.2006.00630.x (**quiz 1943**)
18. Catania RA, Kavic SM, Roth JS, Lee TH, Meyer T, Fantry GT, Castellanos PF, Park A (2007) Laparoscopic Nissen fundoplication effectively relieves symptoms in patients with laryngopharyngeal reflux. J Gastrointest Surg 11(12):1579–1587. https://doi.org/10.1007/s11605-007-0318-5 (**discussion 1587–1578**)
19. Garg SK, Gurusamy KS (2015) Laparoscopic fundoplication surgery versus medical management for gastro-oesophageal reflux disease (GORD) in adults. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD003243.pub3
20. Pearson JP, Parikh S, Orlando RC, Johnston N, Allen J, Tinling SP, Johnston N, Belafsky P, Arevalo LF, Sharma N, Castell DO, Fox M, Harding SM, Morice AH, Watson MG, Shields MD, Bateman N, McCallion WA, van Wijk MP, Wenzl TG, Karkos PD, Belafsky PC (2011) Review article: reflux and its consequences–the laryngeal, pulmonary and oesophageal manifestations. Conference held in conjunction with the 9th International Symposium on Human Pepsin (ISHP) Kingston-upon-Hull, UK, 21–23 April 2010. Aliment Pharmacol Ther 33(Suppl 1):1–71. https://doi.org/10.1111/j.1365-2036.2011.04581.x
21. Ludemann JP, Manoukian J, Shaw K, Bernard C, Davis M, al-Jubab A (1998) Effects of simulated gastroesophageal reflux on the untraumatized rabbit larynx. J Otolaryngol 27(3):127–131
22. Giuliano C, Wilhelm SM, Kale-Pradhan PB (2012) Are proton pump inhibitors associated with the development of community-acquired pneumonia? A meta-analysis. Expert Rev Clin Pharmacol 5(3):337–344. https://doi.org/10.1586/ecp.12.20
23. Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z (2017) Risk of death among users of proton pump inhibitors: a longitudinal observational cohort study of United States veterans. BMJ Open. https://doi.org/10.1136/bmjopen-2016-015735
24. Jobe BA, Richter JE, Hoppo T, Peters JH, Bell R, Dengler WC, DeVault K, Fass R, Gyawali CP, Kahrilas PJ, Lacy BE, Pandolfino JE, Patti MG, Swanstrom LL, Kurian AA, Vela MF, Vaezi M, DeMeester TR (2013) Preoperative diagnostic workup before antireflux surgery: an evidence and experience-based consensus of the Esophageal Diagnostic Advisory Panel. J Am Coll Surg 217(4):586–597. https://doi.org/10.1016/j.jamcollsurg.2013.05.023
25. Ravi K, Katzka DA (2016) Esophageal Impedance Monitoring: Clinical Pearls and Pitfalls. Am J Gastroenterol 111(9):1245–1256. https://doi.org/10.1038/ajg.2016.256
26. Cowgill SM, Gillman R, Kraemer E, Al-Saadi S, Villadolid D, Rosemurgy A (2007) Ten-year follow up after laparoscopic Nissen fundoplication for gastroesophageal reflux disease. Am Surg 73(8):748–752 (**discussion 752–743**)
27. Fumagalli U, Bona S, Battafarano F, Zago M, Barbera R, Rosati R (2008) Persistent dysphagia after laparoscopic fundoplication for gastro-esophageal reflux disease. Dis Esophagus 21(3):257–261. https://doi.org/10.1111/j.1442-2050.2007.00773.x
28. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID (2003) Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). Thorax 58(4):339–343

Review

Eur Surg 2016 · 48:74–91
DOI 10.1007/s10353-016-0385-5

european surgery
ACA Acta Chirurgica Austriaca

Laryngopharyngeal reflux: diagnosis, treatment and latest research

G. L. Falk[1,2,3] · **S. J. Vivian**[4]

Received: 13 December 2015 / Accepted: 13 January 2016 / Published online: 25 February 2016

Summary
Aim A review of the recent changes in understanding of laryngopharyngeal and extra-oesophageal reflux symptoms.

Method Literature search over 7 years (2008–2015) and relevant historical cited articles.

Results Modern investigation more clearly shows a subgroup of patients with intermittent full column oesophago-gastric-reflux-causing symptoms. Multiple other sites in the lung, head and neck may also be implicated in the reflux disease process.

Conclusion Understanding of extra-oesophageal reflux symptomology is evolving. New equipment and techniques suggest further areas of research, and as yet effective therapy remains elusive for some.

Keywords Laryngopharyngeal reflux · Gastro-oesophageal reflux · Laparoscopic fundoplication

G. L. Falk, MBBS, FRACS (✉)
Suite 29, 12-18 Tryon Rd,
NSW 2070 Lindfield, Australia
e-mail: sydney.heartburn@gmail.com

G. L. Falk, MBBS, FRACS
University of Sydney,
Sydney, Australia

G. L. Falk, MBBS, FRACS
Macquarie University,
Sydney, Australia

S. J. Vivian, BA
Sydney Heartburn Clinic,
Lindfield, Australia
e-mail: sarahjaynevivian@gmail.com

Aim

Review the recent changes in the evaluation of cause, investigation and therapy in the evolving area of extra-oesophageal symptoms of reflux disease.

Method

Ongoing review of the literature has been pursued by the senior author (GLF) of PubMed and the National Centre for Biotechnology Information (NCBI) at the National Library of Medicine (NLM). Search was conducted monthly using ("laryngopharyngeal reflux"[MeSH] OR LARYNGOPHARYNGEAL REFLUX[Title/Abstract]) OR ((COUGH[Title/Abstract] OR "cough"[MeSH]) AND ("gastroesophageal reflux"[MeSH] OR "GASTROESOPHAGEAL REFLUX"[Title/Abstract] OR "GASTROOESOPHAGEAL REFLUX"[Title/Abstract] OR "gastroesophageal reflux"[MeSH Terms] OR REFLUX[Title/Abstract])) for the years 2008–2015. Relevant articles were extracted progressively and topics searched on PubMed as required from 2008 onward. Further searches were conducted for (GASTROESOPHAGEAL REFLUX[MESH] OR LARYNGOPHARYNGEAL REFLUX[MESH] OR REFLUX) AND IMPEDANCE and ("Barrett Esophagus"[MAJR] AND DYSPLASIA) OR ("Barrett's dysplasia") OR (Barrett*[ti] AND DYSPLASIA[ti]).

Bibliographies of multiple articles contained further article references from earlier years and have been utilised selectively in discussion. The references were then utilised to elucidate the multiple topics addressed in the review. Criteria for selection were relevance, English language, and publication in reputable peer-reviewed journals unless of substantial significance.

The spectrum of gastro-oesophageal reflux disease

Reflux disease, in its various forms, affects a large group of society. Typical gastro-oesophageal reflux disease (GORD) affects at least 10% of individuals in Western society [1]. And it has been estimated that about 10% of ear, nose and throat specialty (ENT) workload reflects possible atypical reflux patients [2]. While typical reflux disease has long been relatively easy to diagnose both symptomatically and on testing, extra-oesophageal disease is still not adequately diagnosed, and treatment is fraught. Further, it is recognised there is a lack of a gold standard diagnostic test ([3], p. 37). There are limitations in the diagnostic equipment and physiological understanding of the illness, and the symptoms are non-specific. Unsurprisingly, surgery for laryngopharyngeal reflux (LPR) has been dogged by poor results in contradistinction to the good results obtained in refractory standard reflux disease. This review attempts to deal with some matters of standard reflux disease and surgery as well as the pathophysiology and management of LPR.

Symptoms

The Montréal criteria largely recognises GORD by cardinal symptoms of heartburn and fluid regurgitation, usually considered more than once or twice per week [4]. The Montréal definition also recognises atypical or extra-oesophageal reflux disease where symptoms merge into the laryngopharynx, nasopharynx and lung and dental erosion. Even this distinction is not simple; water brash (the phenomenon of increased salivation) is often misinterpreted by clinicians, and post nasal drip syndrome is confusing to patient and clinician. Severe standard reflux can be associated with LPR symptoms and pulmonary aspiration and usually reflects severe disease often in the supine position with gross flooding of the oesophagus. This is quite different from LPR disease where heartburn and regurgitation are “silent” or less prominent. Alarm symptoms such as the dysphagia or odynophagia (pain on swallowing), anaemia, haematemesis or weight loss must be identified expeditiously to exclude the onset of malignant complication.

Typical gastro-oesophageal reflux disease

This condition is largely identified by the presence of symptomatology of heartburn and regurgitation and occasional dysphagia in the presence of oesophagitis. It is recognised that 15–20% of the adult population in Australia will suffer heartburn more than once per week [5]. This is similar to studies from the USA and one would expect throughout the Western world [1]. The burden of disease in the community is therefore quite substantial.

Pathophysiology

The anomalousness of reflux disease hinges around the abnormal frequency or duration of exposure to gastric contents within the tubular oesophagus. There is a balance between mucosal attack and the mucosal defences and between clearance of the oesophagus and frequency, volume and concentration of reflux fluid. In lesser cases of reflux disease, transient lower oesophageal sphincter relaxation occurs (TLOSR) [6] and the trans-diaphragmatic pressure gradient allows fluid to pass upwards into the oesophagus to be cleared by secondary peristalsis. Should the gradient be great, such as in chronic pulmonary disease or obesity, reflux may be increased. Delayed gastric emptying in the reflux patient is frequent and may exacerbate reflux exposure. Peristalsis may be deficient [7, 8] and the oesophagus not clear normally. Mucosal resistance may be diminished such as in patients on prostaglandin inhibitors, chemotherapy, steroids or having a chronic medical illness. Loss of tight junction integrity may play a role in symptomatology [9–11]. More severe disease may become evident with the presence of a hiatus hernia [12] and absolute reduction in the lower oesophageal sphincter tone [13, 14] with increasing levels of reflux fluid within the oesophagus and increasing levels of oesophagitis evident at endoscopy [15].

Complications

Oesophagitis and the oesophageal ulceration are complications of reflux of gastric content. Continued inflammation may lead to the development of scarring and strictures, deep ulceration and haemorrhage, inhalation of gastric contents causing aspiration pneumonia and the development of Barrett’s oesophagus and subsequent risk of carcinoma. Barrett’s mucosa may pass through the typical metaplasia-dysplasia-carcinoma sequence. The risk of reflux causing carcinoma has been well recognised especially demonstrated in a seminal article by Lagergren et al. where the duration and severity of symptoms was positively associated with increasing rates of oesophageal adenocarcinoma (Figs. 1, 2; [16]).

Diagnosis

Historically, the diagnosis of reflux disease has largely been based on the symptoms of heartburn and regurgitation. The response to therapy has been measured against control of these symptoms. Symptomatic diagnosis continues to be the recommendation of most gastroenterology societies probably due to the lack of sensitivity of endoscopy to diagnosis [17]. This recommendation continues despite good study (the Diamond Study) showing a sensitivity and specificity of the symptomatic diagnosis of GORD of 62 and 67%, respectively [18].

Objective diagnosis has hinged around performance of endoscopy or response to proton pump inhibitor

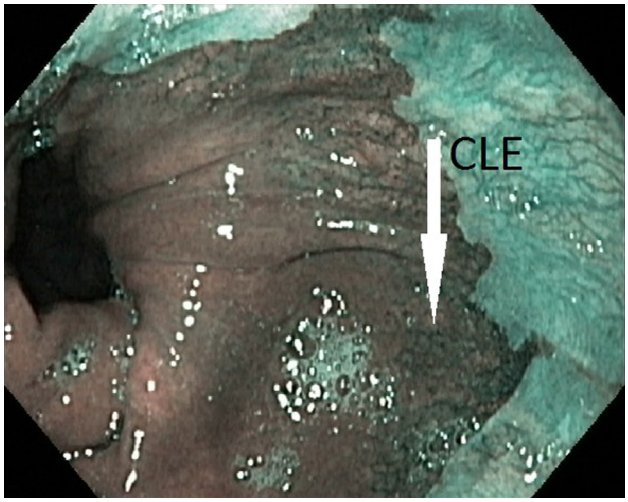


Fig. 1 Columnar lined oesophagus under narrow band imaging: biopsies showed no dysplasia. *CLE* columnar lined oesophagus

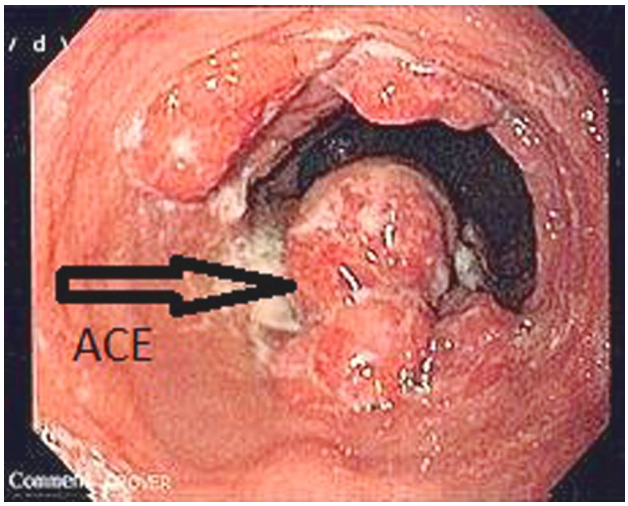


Fig. 2 Hemicircumferential polypoid tumour lower oesophagus: biopsies showed adenocarcinoma. *ACE* adenocarcinoma oesophagus

(PPI). Various gastroenterology societies have recommended a trial of PPI, enabling the practitioner to treat by medication. Endoscopy is not recommended initially for heartburn and regurgitation. Only if the patient requires ongoing therapy to control symptoms (refractory disease) is endoscopy recommended [5]. The so-called PPI test has been fashionable in the clinical diagnosis of GORD for a considerable period. Trust in this "test" is largely fallacious, having been shown in the Diamond Study that "symptomatic response to esomeprazole was neither sensitive nor specific for diagnosis of GORD" [18].

Endoscopy has been recommended for alarm symptoms of dysphagia, odynophagia, haematemesis or weight loss and anaemia. Additionally it is recommended if the diagnosis is unclear, where symptoms persist or are refractory to treatment, and when complications are suspected [19]. However, it has been demonstrated that

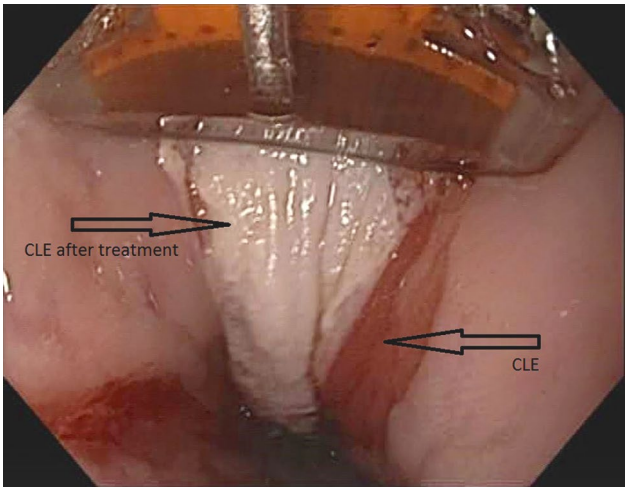


Fig. 3 HALO 90 radiofrequency ablation (RFA) for endoscopic treatment, as described in the text

only about 9 % of patients are diagnosable by endoscopy once PPI is commenced. Its use is therefore largely for the exclusion of alternative diagnosis. A positive diagnosis of reflux can be made before treatment in up to 50 % of patients by mucosal change. To these indications for endoscopy, one could add male sex, age over 40, change in symptomatology and length and severity of symptoms possibly predictive of the development of carcinoma [16]. The rate of adenocarcinoma of the lower oesophagus is increasing in Western civilisation [20, 21].

Surveillance of patients identified with Barrett's oesophagus is frequently recommended [5]. It is therefore worthwhile identifying the presence of Barrett's oesophagus for purposes of prevention of dysplasia or carcinoma development. Radiofrequency ablation management by endoscopy has proven safe and effective for dysplasia in expert groups [22–24]. Guidelines for management of Barrett's dysplasia and superficial carcinoma are published (Fig. 3; [25–27]).

Oesophagitis has been the mainstay of the diagnosis of reflux, but only 50 % of patients with heartburn and regurgitation will demonstrate any such acute change (picture of oesophageal grading). It is graded according to the Los Angeles classification, which reflects the severity of reflux exposure and degree of damage and indirectly the healing rates of medical therapy (Figs. 4, 5, 6).

Hiatus hernia may be demonstrated but does not confirm reflux disease diagnostically. The gold standard diagnostic test for reflux disease has been a 24-h pH study [28], but more recently it has become evident that symptoms may occur due to non-acid reflux disease [29]. The advent of impedance technology (tube study combined with pH) identifying gas and non-acidic fluid as well as acidic fluid has added to the understanding of physiology of this illness. This information may be displayed by colour plot graphic (Figs. 7, 8; [30]). Automatic reporting may help guide the clinician to relevant "episodes" which can be confirmed or deleted. Biopsy of the oesophagus showing inflammatory cell infiltrate is not diagnostic of

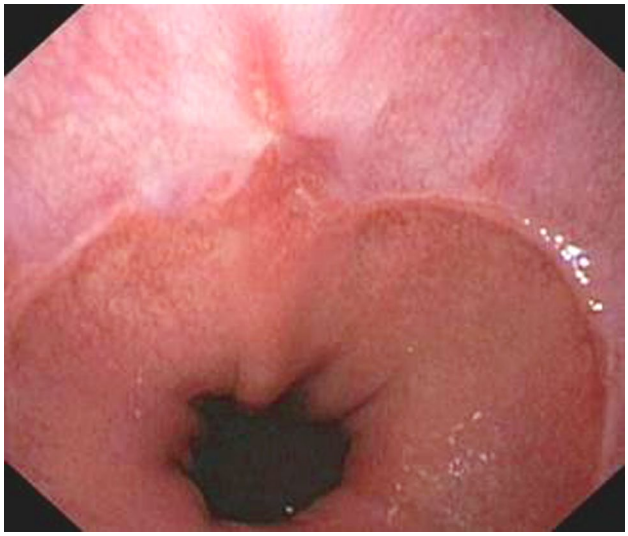


Fig. 4 Oesophagitis—grade A

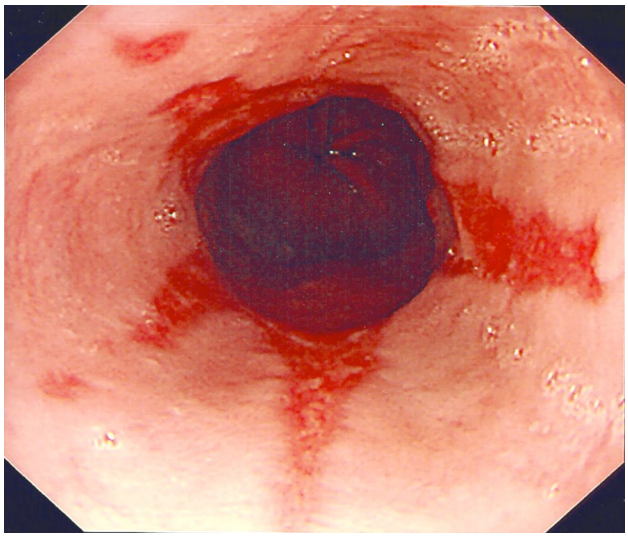


Fig. 5 Oesophagitis—grade B

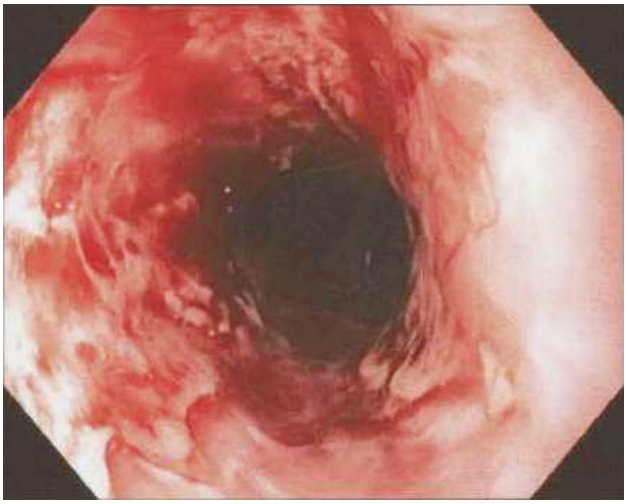


Fig. 6 Oesophagitis—grade C

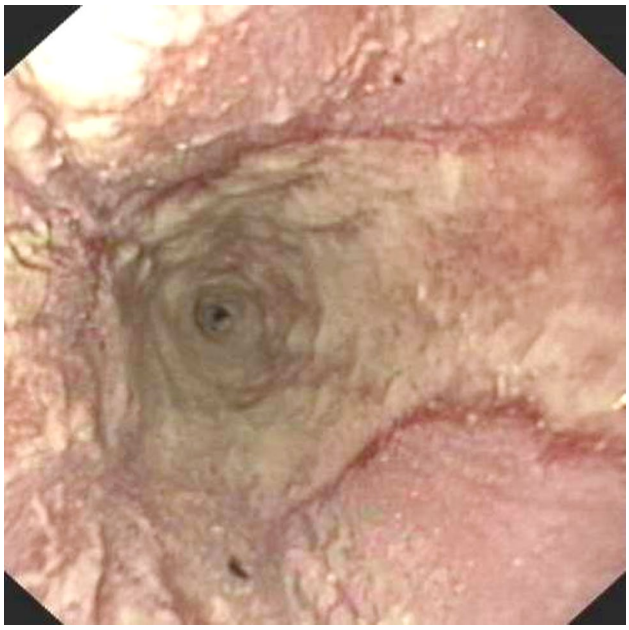


Fig. 7 Oesophagitis—grade D

reflux but can exclude eosinophilic oesophagitis as an alternative.

DeMeester and Johnson initially developed a scoring system of diagnosis of reflux [28]. This has largely become the standard for diagnosis, utilised in patients where it had been unclear or prior to surgery to reduce failure of surgical therapy. Use of 24-h pH study may enable diagnosis in the patient group without oesophagitis, resistance to medical therapy or after commencement of therapy. A small tube is passed trans-nasally, and electrode and sensor are fixed 5 cm about the cardio-oesophageal junction (COJ). Results are compared with established normals. Results are recorded by a data logger over a 24-h period. More recently, the Bravo device (Given Imaging Ltd., Yoqneam 20692 Israel) has achieved similar results when placed by a remote transponder attached to the oesophageal wall [31]. Increasing levels of acid exposure, as seen by the 24-h pH study, show progressive change in grading of oesophagitis. The Los Angeles classification system for oesophagitis is universally recognised [32].

Medical treatment Lifestyle manoeuvres, loss of weight and antacid are commonly utilised and either single or double dose proton pump in addition (PPI). Approximately 30 % of patients will have troublesome breakthrough symptomatology on this therapy, and 10–20 % of patients will have unhealed oesophagitis [1, 19, 33, 34]. General practice (family doctor) interview of these patients infrequently identifies breakthrough symptoms such as atypical chest pain or nocturnal proximal regurgitation symptoms, and the lack of efficacy of PPI is frequently undetected. Sometimes the lifestyle management and dietary restrictions grossly affect the quality of life of the patient and are frequently not considered. For

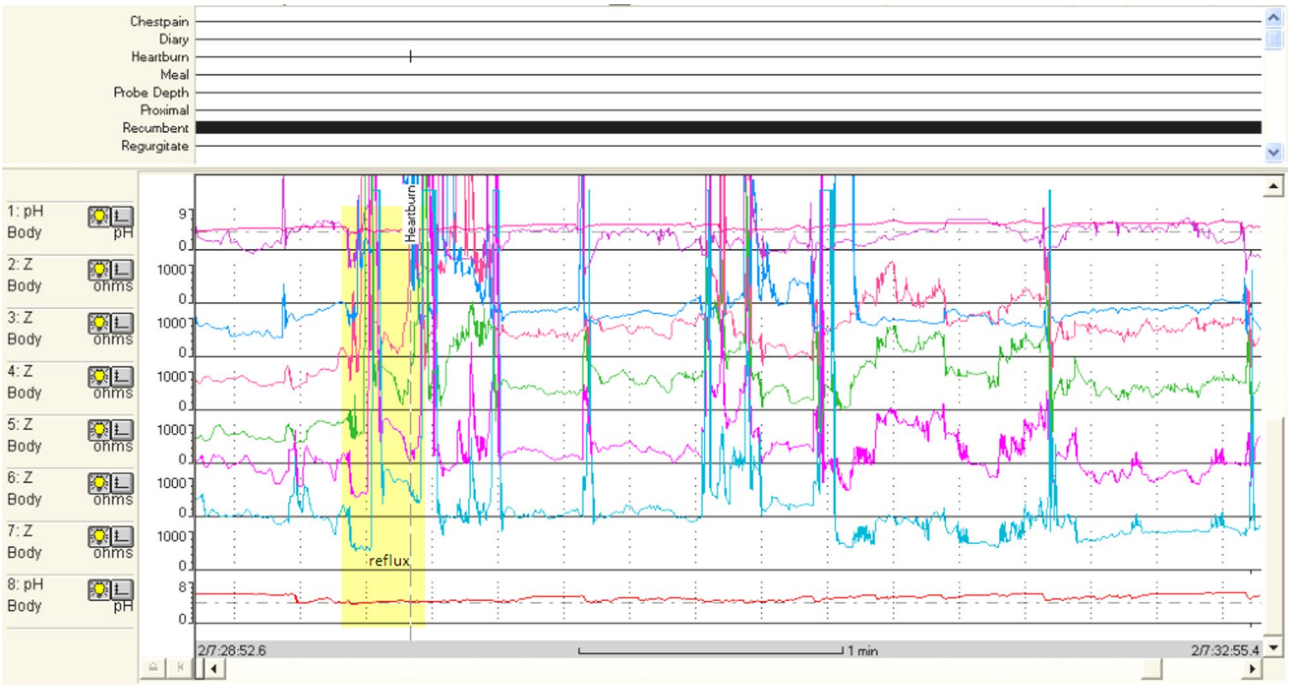


Fig. 8 Graphic representation of impedance study. The *yellow area* indicates reflux, and the tracings indicate change in impedance across electrodes. The simplicity of the Klaus graph (Figs. 16, 17) is highlighted

patients failing PPI, nocturnal H_2 antagonists have been recommended, but data now indicate the duration of efficacy is measured only in weeks [29].

Despite generally perceived safety of PPI therapy, it is emerging that there may be side effects at double dose and real rates of adverse events, including osteoporotic fracture, increased pneumonia and bowel infection [19, 36], and a recent report shows possible association with myocardial infarction, with or without clopidogrel use [37].

Surgical treatment It has been calculated by the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) organisation in the USA that approximately 30 % of reflux patients experience inadequate medical therapy and are therefore candidates for surgery [38]. Surgery is however only pursued in approximately 3 % of those patients leaving an enormous gap in therapeutic management and large numbers of patients with continued symptoms of oesophagitis. These patients would be represented in the area above the curves (Figs. 9, 10). The indications for surgery generally have been failure of medical therapy for symptoms or oesophagitis.

Before performing surgery, the oesophageal diagnostic advisory panel [39] recommended endoscopy and considering reflux diagnostic with grade C or D oesophagitis or long segment Barrett's oesophagus confirmed. Manometry and oesophageal pH monitoring were recommended in patients other than those diagnosed on the criteria above. High-resolution manometry at this stage has not been considered indicated for assessment for antireflux surgery [1]. Surgery is now predominantly performed by laparoscopy (laparoscopic antireflux surgery, LARS) and is most frequently a 360° fundoplication. The so-called tailored approach to ineffective oesophageal motility (IEM) has not been shown scientifically necessary [1].

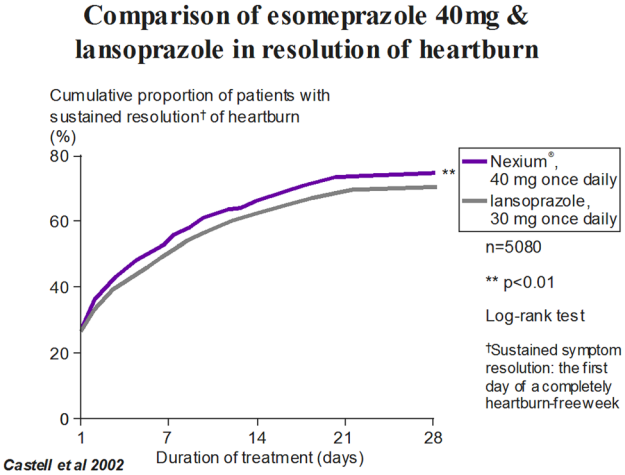


Fig. 9 Comparison of esomeprazole 40 mg and lansoprazole in resolution of heartburn. Maximal effective response to medication, 75 % [35]

Surgical outcome has been repeatedly demonstrated by meta-analysis and systematic review to exceed that of medical [40]. Despite these proven outcomes, there continues to be substantial discussion amongst the medical community (non-surgical) about the potential for side effects and revision surgery. Reduced mobilisation of the fundus and some partial fundoplication techniques have improved effective outcome beyond the initial operation of Rudolf Nissen [41]. While fundoplication commonly

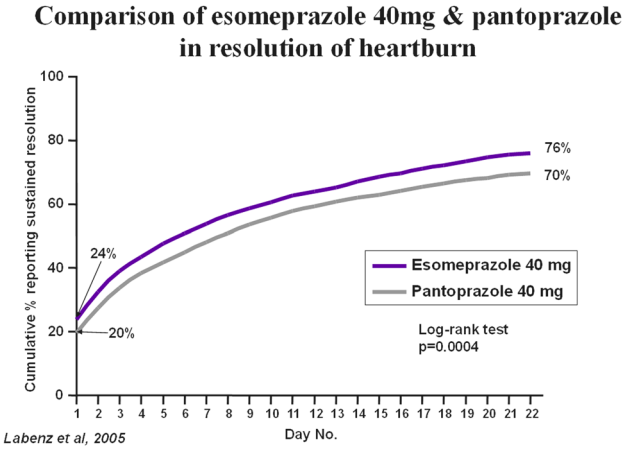


Fig. 10 Comparison of esomeprazole 40 mg and pantoprazole in resolution of heartburn. Maximal effective response, 70–76 % [34]

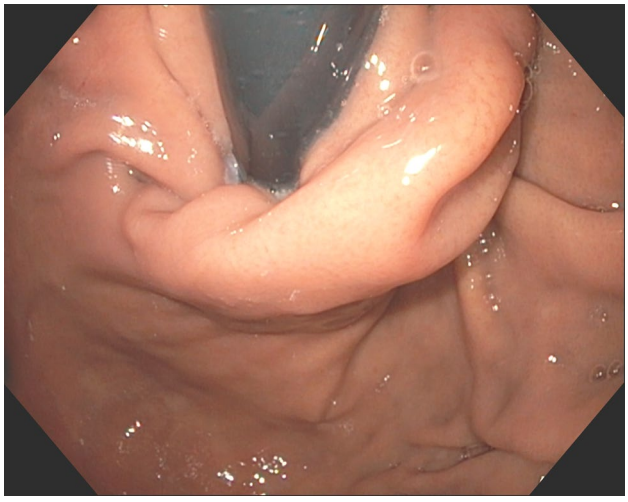


Fig. 11 Endoscopic retrograde view of fundoplication in cardia

bears this eponym, it has passed through several iterations and in most hands is generally quite different from that originally described. Recently in this journal, Kristo et al. [42] have argued for specialised centres of excellence to obtain adequate improved outcomes (Figs. 11, 12).

Some endoscopic antireflux therapies are showing promise [38]; however, many other techniques while initially appearing favourable have not stood the test of time. It remains to be seen whether these new techniques such as Linx® (Torax Medical, St Paul MN 55126, USA), where a magnetic cuff is placed around the COJ, or trans-oral incisional fundoplication (TIF: Endogastric Solutions, Remond WA 98052, USA) ultimately pass the test of time. Comparison by randomised controlled trial against medical and surgical therapy has not been adequate. Multiple other endoscopic techniques were initially greeted with enthusiasm by the non-surgical gastroenterology community and tended only to be judged

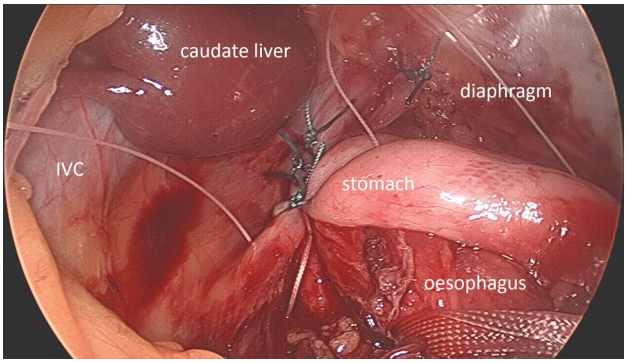


Fig. 12 Laparoscopic view of fundoplication under construction. *IVC* inferior vena cava

by partial symptomatic outcome and incomplete, inadequate objective study and rapidly disappeared from use (EndoCinch: Bard, Murray Hill NJ, USA; Enteryx: Boston Scientific, Malborough Mass, USA; Enteryx injectable polymer). Stretta® (Mederi Therapeutics Inc, Greenwich CT 06830 USW) continues under some investigation.

Atypical reflux disease

(Alternative terms: extra-oesophageal/supra-oesophageal/laryngopharyngeal reflux disease, LPR)

There are several recognised atypical reflux syndromes described by the Montréal classification as laryngeal, cough, asthma and dental [4]. We would propose that some sinus disease and middle ear infection may well be also become recognised as separate syndromes. Nasopharyngeal reflux was demonstrated by DelGaudio [43]. Improvement in chronic sinusitis has been noted with reflux therapy [44].

Symptoms frequently associated with a laryngeal and pharyngeal diagnosis of reflux include a globus sensation, frequent throat clearing, cough, hoarseness, throat pain and excessive mucus in the throat. Sinus symptoms may be recognised as nasal discharge, central or lateral facial pain, earache, ear dullness and episodes of infection. Dentists now frequently describe loss of tooth enamel as being related to reflux [4, 45–49]. Gross pulmonary aspiration has been recognised in a small percentage of patients for a considerable amount of time. Reflux is strongly implicated in the rejection of lung transplant grafts, and antireflux surgery makes more than a 20 % difference to graft survival [50–54]. What is not readily apparent however are lesser grades of pulmonary reflux disease, which are less symptomatic and perhaps are implicated in pulmonary fibrosis, bronchiectasis, occasional lung infection and an asthma-like syndrome. Reflux cough syndrome is particularly well recognised [55–58].

Many patients do not describe typical heartburn and regurgitation. This condition, because of the lack of heartburn, has been often described as “silent” reflux. The Diamond study identified 49 % of patients having

atypical symptomatology in a community-based study [18].

Complications in all these organs may occur with onset of vocal granuloma, voice change interfering with work, excessive cough-reducing quality of life, sinus infection, dental caries, early infection often requiring surgery in children, asthma and hospital admission, gross pulmonary infection and pulmonary damage and is implicated in the loss of graft in the lung transplantation [4, 19, 59–64]. There is concern that some dysplasia and carcinoma of the larynx may also be reflux related [65].

Pathophysiology of atypical reflux symptoms

Potentially damaging substances are present within reflux fluids which may cause damage within the pharynx including acid, pepsin, bile salts, bacteria, pancreatic proteolytic agents and pepsin (remaining active pH up to 6 [66]). Pepsin has been demonstrated in the laryngeal mucosa and middle ear fluid [67, 68].

IEM and poor oesophageal clearance are strongly associated with atypical proximal symptomatology [69–75]. A recent study in our group has shown that reduction in clearance in the oesophagus measured by impedance is predictive of proximal reflux identified in scintigraphic studies [76]. Such clearance abnormally was also closely correlated with worsening peristaltic function of the oesophagus.

Additionally, an oesophago trachea neural mediated bronchial reflex mechanism has also been suggested with experimental supportive evidence from several authors [77, 78]. It has been the "Concord group" (see Appendix) experience that a significant proportion of patients with proximal reflux do not have heartburn and are so traditionally designated "silent" perhaps due to medicine's ignorance of this entity [69, 77, 79, 80]. Multiple researchers however are aware of this "silent" phenomenon, as interestingly is the patient population, even if the illness is treated with scepticism by conventional medicine [55, 81–83].

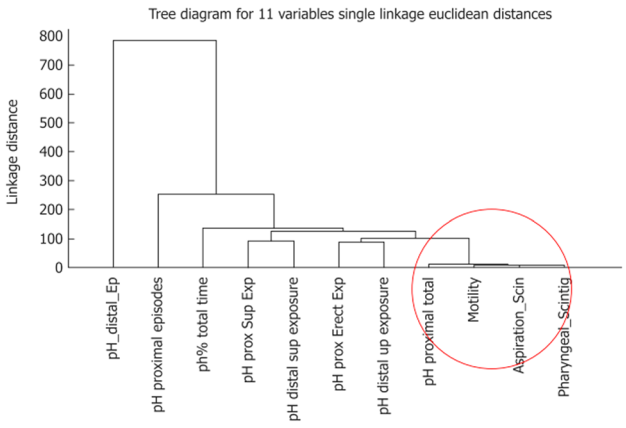


Fig. 13 Physiological factors associated with laryngopharyngeal reflux symptoms—a cohort study [86]

Reduced cough threshold has been identified in genesis of symptomatology and has been demonstrated by capsaicin testing and other irritant agents; it is associated with non-acid reflux on impedance studies [84, 85].

Falk et al. (Fig. 13; [86]) reported a tight correlation demonstrated by cluster analysis suggesting possible physiological causes of proximal reflux disease. Patients with a strong clinical likelihood of LPR were investigated by two channel impedance 24-h pH study and a standardised reflux scintigraphic study. Strong association was found between increasing levels of proximal acid exposure, diminished oesophageal motility, scintigraphic pulmonary aspiration and scintigraphic pharyngeal contamination raising the prospect of a pathway for further investigation.

Diagnosis

Atypical symptoms

Atypical symptoms are largely non-specific and may arise due to non-reflux causes from the head and neck, trachea and bronchus, pulmonary substance, medications and generalised systemic disorder. This makes it extremely difficult to identify and diagnose a homogenous patient group which is a likely cause of the difficulty in finding an adequate treatment due to lack of a diagnostic gold standard [3].

Many practitioners and studies have called into question the very existence of supra-oesophageal reflux disease [87, 88]. However supra-oesophageal reflux disease has now been included in the classification of Montréal [4, 18]. Symptoms score has been widely utilised in ENT [89, 90].

Laryngoscopy

Signs of inflammation may be identified in the larynx and pharynx and have been attributed to chronic LPR disease. Consistent guidelines and consensus for the diagnosis of LPR is lacking [91]. Laryngeal signs for LPR considered by ENT surgeons as suggestive of diagnosis are posterior laryngeal erythema, intra-arytenoid bar and cobblestoning, oedema and granuloma [91]. However, high intraobserver error rates have been identified in this area [92], and these changes have been observed in many normal volunteers [93, 94]. Laryngoscopy findings therefore have largely been demonstrated not accurate due to intraobserver variability [92, 95, 96] and lack of sensitivity [97]. A 2007 study by Vavricka showed no difference between normals and the atypical reflux group [98]. However, Habermann et al. [90] have seen substantial clinical value in a blinded cohort study using ENT symptoms and examination. Belafsky et al. [99] have demonstrated some reliability of a scoring system of examination (Fig. 14).

This uncertainty has largely lead to the recognition that laryngoscopy as a diagnostic tool is limited to perhaps the most severe changes of laryngeal inflammation

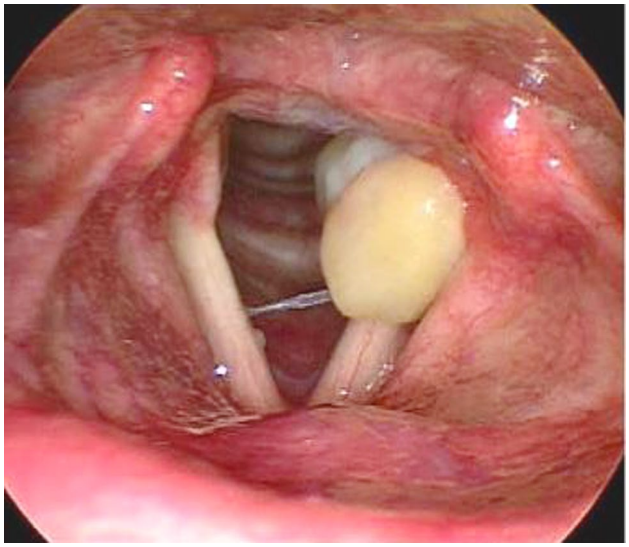


Fig. 14 Laryngoscopic image of a vocal granuloma [100]

including granuloma, subglottic stenosis and dysplasia [93].

Gastroscopy in atypical reflux disease

Reports have demonstrated that less than 30 % of patients with extra-oesophageal manifestations of reflux have oesophagitis [91, 101]. Clearly distal oesophagitis does not discriminate which individual has proximal reflux and so cannot be utilised for the presence of proximal reflux or identification of reflux in the pharynx or lung. Changes seen in passing the larynx by gastroenterology must be discounted in a similar fashion to laryngoscopy. Similarly, visualisation of oesophageal erythema has never been diagnostic of reflux. Biopsy, while it may exclude diagnosis like eosinophilic oesophagitis, is also not diagnostic of reflux disease proximally or distally. Gastroscopy therefore is of limited diagnostic use in LPR patients apart from exclusion of other diseases.

Tube-based studies

The 24-h PH study may be considered to have been the gold standard for diagnosis of typical reflux disease in the past; however, there continues to be controversy about the value of pH recording in the proximal oesophagus. Vaezi et al. [101], Vakil et al. [4] and Koufman [102] report the sensitivity of oesophageal and pharyngeal monitoring of pH ranging from 50 to 80 % making diagnosis doubtful. There remains an intrinsic deficiency of pH recording reflux as it measures acid as a surrogate of reflux fluid. Acid is lacking in many episodes of reflux proximally as neutralisation occurs and a variable number of reflux episodes are non-acid at outset. Measurement of acid is therefore a poor surrogate for the detection of the presence of refluxed fluid (Figs. 15, 16).

The advent of intraluminal impedance and 24-h PH monitoring was initially greeted with enthusiasm for a potentially better ability to diagnose LPR due to the ability to identify both acid and non-acid reflux events [103].

Poor correlation however has been shown between laryngeal changes thought to be due to reflux and impedance pH studies [97, 104]. Normal proximal oesophageal values are in dispute with substantial difference in values in different series [39, 105, 106]. The situation is not definitive, and a diagnostic test for proximal reflux and laryngopharyngeal symptoms remains elusive. Use of a pharyngeal recording site is being trialled but is defective on a number of counts including a lack of identifiable normal values, substantial intraobserver variability [107] and difficulty placing the catheter accurately. Further study will be required to determine the predictive value of results obtained by this technique. Nasal secretions can be acidic.

PPI test

While a response to PPI has been considered by some to indicate the presence of reflux disease in the laryngo pharynx, the Cochrane review [108] found no high-quality trials, and a systematic review and meta-analysis failed to demonstrate superiority of PPI over placebo in the LPR patient group [109–111].

Exclusion of other diseases

Exclusion of other diseases is required (pulmonary, smoking, allergies, postnasal drip, other laryngeal disease, pharyngeal infection, vocal abuse, environmental irritants, alcohol abuse, viral disorder, drugs, psychosomatic depression) to name but a few [112]. Laryngopharyngeal syndromes can be more confidently predicted if postnasal drip, medical cause of cough, smoking, abnormality on chest X-ray and stable management of asthma are excluded. In this circumstance, a multidisciplinary approach is practically found to be of value in selecting a group of patients with a higher pretest probability of reflux-caused abnormality. A multidisciplinary approach of ENT, respiratory medicine, oesophageal physiology and surgery may be clinically valuable and has certainly been the “Concord group” experience.

Experimental

Pepsin testing

Pepsin has been found in the middle ear of children with otitis media [64]. Pepsin may also be assayed from saliva and from bronchial lavage. A pepsin assay (Peptest™: RDBiomed Limited, Hull HU16 5JQ, UK) is now available, but techniques of collection and sites have yet to be proven of clinical value [113–116]. Nonetheless, it continues to raise the likelihood that proximal reflux disease can cause many different phenomena.

Pepsin tests and bile acids have been investigated in studies in probable reflux cough patients to identify gas-

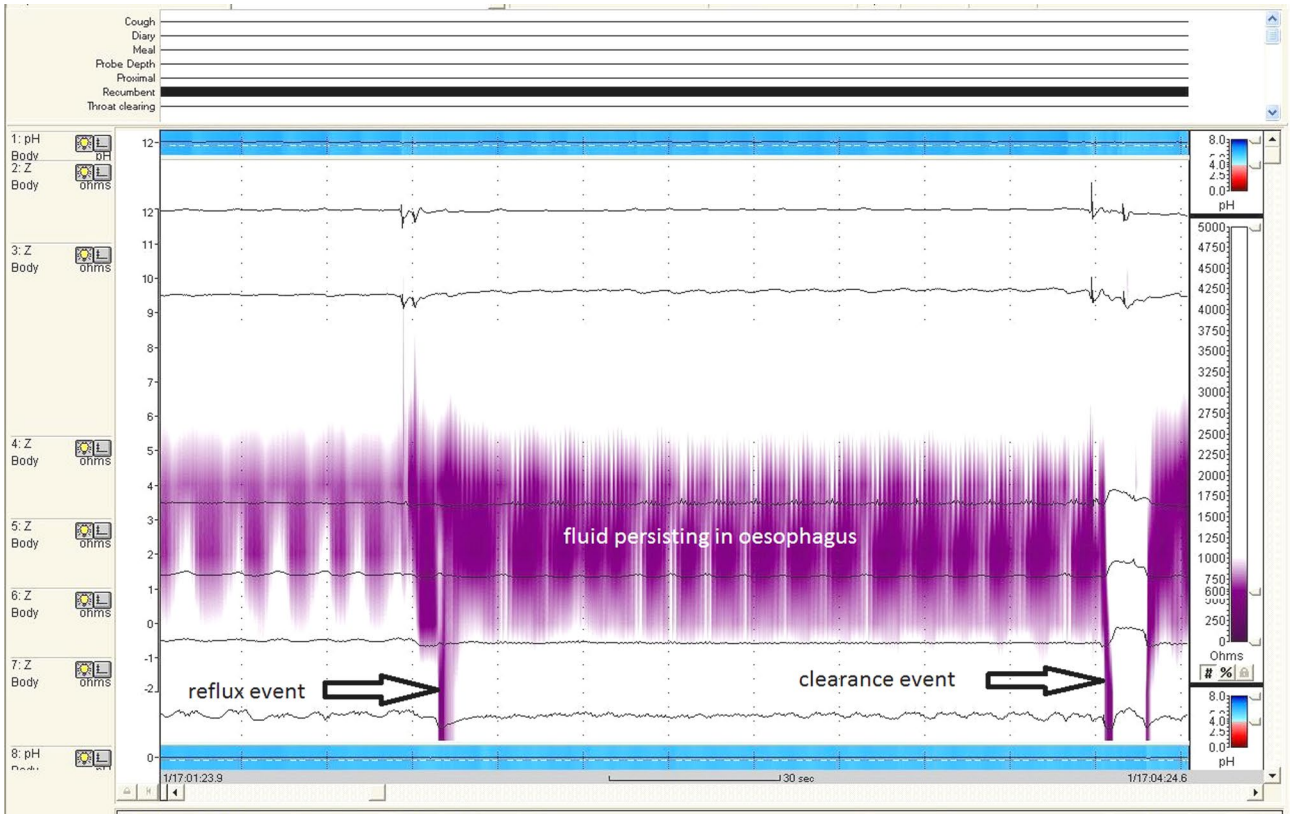


Fig. 15 Colour plot graphic of impedance tracing; delayed clearance of fluid in the mid-oesophagus

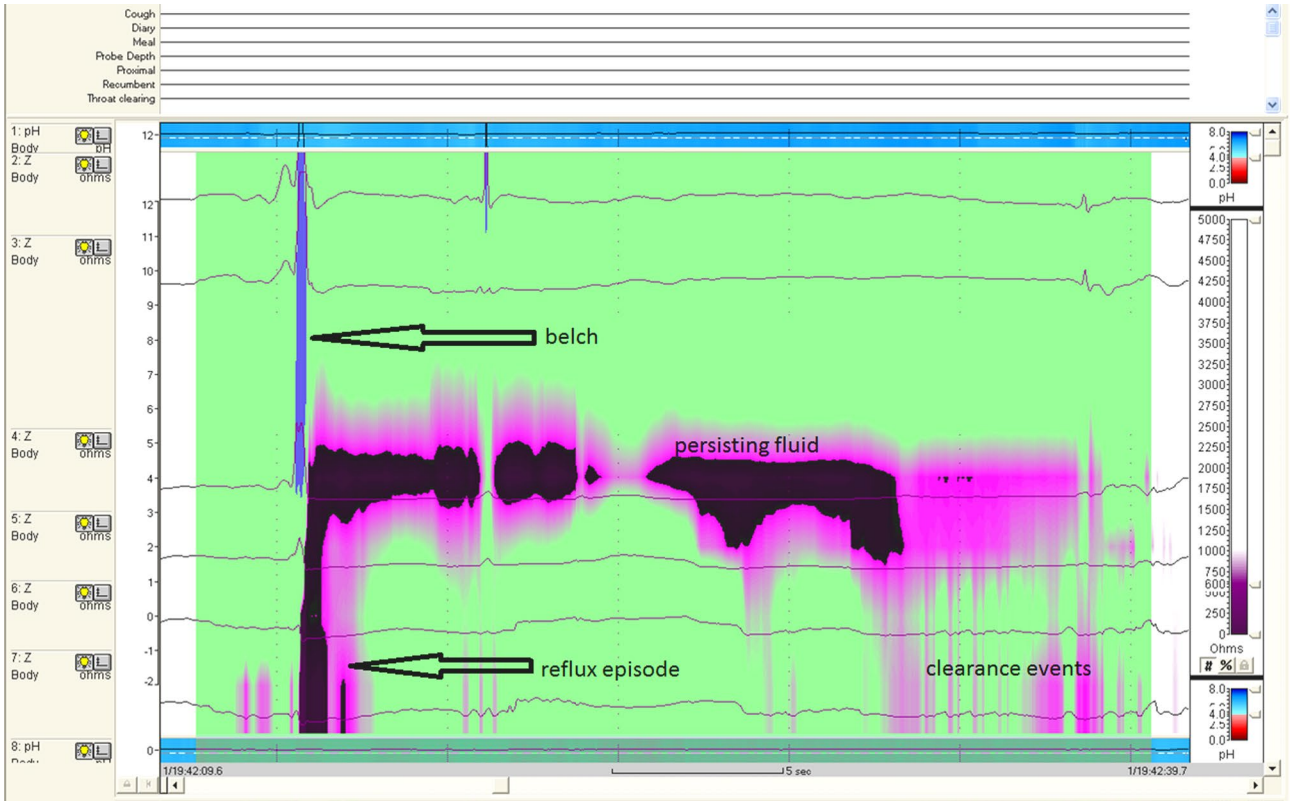


Fig. 16 Colour plot graphic of belch followed by poor reflux clearance 30 s. *Blue* vertical is belch followed by reflux of fluid

tric contents in the regions outside the stomach. Both sputum and bronchial lavage have been investigated. Studies have not demonstrated a difference between healthy controls as yet [50, 117–119]. The usefulness of this test remains uncertain in cough and pulmonary disease. Pepsin has been identified in the middle ear aspiration fluid especially in neonates suggesting a cause for a subset of middle ear infection [64, 113, 114, 120]. In the future, this test may prove to be sensitive and specific for diagnosis of LPR disease [121, 122].

pH pharyngeal catheters

Standard catheters in the pharynx are considered inaccurate [123–125], but meta-analysis suggested it may be of value [126]. New devices are under development due to the inaccuracy of standard catheters placed in the pharynx due to the artefact from movement and the drying of the electrode (ResTech, San Diego, CA 92127) [127]. No clinical data are available, and the usefulness of this has to be considered limited as it is apparent that much proximal reflux is non-acid and so will not be evident on acid (pH) pressure alone. Low-acid and non-acid fluids are increasingly being recognised by clinicians as being symptomatic in some patients [128–130]. Even if the new pH devices are able to accurately register acid in the pharynx, they remain intrinsically inaccurate due to the acid pressure being variable in reflux fluid [131].

Scintigraphy

Identification of fluid from the stomach above the cricopharyngeus may select a group of patients with reflux-mediated extra-oesophageal symptoms. Isotope in gastro-oesophageal fluid has an intrinsic potential value as it can be traced and is not susceptible to artefact, drying or movement as are the catheter-based tests. It does not require the presence of acid as a "marker" of the presence of reflux fluid. It is a positive identifier of gastric fluid. Scintigraphy for reflux has been utilised in children for many years, and modifications of these techniques have been shown to provide good details of GORD and lung aspiration [79, 132–138]. Results vary depending upon technique [133, 135, 137, 138]. Standardisation of technique therefore is vital for reproducibility of this test. Results in our series [139] are similar to the study of Bestetti et al. [140]. Symptoms were also tightly correlated with pharyngeal exposure in our report [139]. Usefulness of this technique remains to be proved but may obviate invasive intrinsically misguided (testing for acid) and inaccurate tests (intraobserver variability) but requires a particular standardised technique with the rigid approach to methodology and preparation of contrast.

Scintigraphy has the ability to show pulmonary and pharyngeal reflux (Fig. 16b, 17a) and can show temporal accumulation of reflux in the pharynx (Fig. 18) predictive of symptoms and lung disease [139].

Medical treatment

Lifestyle modification

Pearson [141] has demonstrated dietary and behaviour modification to be effective in typical reflux management and reduction of weight in the obese being demonstrated to improve gastro-oesophageal reflux symptoms [142, 143]. The effectiveness of weight loss does however remain controversial, and whether it improves objective measures is uncertain. There is little evidence that lifestyle change demonstrated in typical gastro-oesophageal reflux symptomatology also benefits the atypical LPR group.

PPI

While theoretically an attractive treatment, episodes of reflux high in the oesophagus are saliva and relatively non-acidic fluid by the time of passage to the upper oesophagus. Recent meta-analysis of randomised trials demonstrated little advantage over that of placebo in patients with suspected chronic laryngitis from reflux [111]. Similarly in a review by Reimer and Bytzer, no difference was convincingly shown between the PPI therapy and placebo in randomised control study [144]. Addition of nocturnal H_2RA has not been shown effective [145, 146].

Reflux inhibition

Lesogaberan has been shown to reduce the rate of transient lower oesophageal sphincter relaxation [147], but is of uncertain clinical effect and in our experience has not made a great deal of difference to LPR symptoms, although baclofen has been shown to decrease acid reflux events and acid exposure [148, 149]. However, use of baclofen has been limited by side effects in our experience. Results overall have been disappointing in association with PPI [147, 150]. Further studies require objective scores for cough to identify treatment affects more accurately [151]. Baclofen may theoretically benefit reflux cough by inhibition of the reflux and cough effect [152–155].

Prokinetic

Prokinetic agents while theoretically beneficial have not been shown to be of any value in LPR disease [141]. A recent systematic review found articles giving conflicting evidence regarding the effectiveness of prokinetic agents and were not able to make recommendations [156].

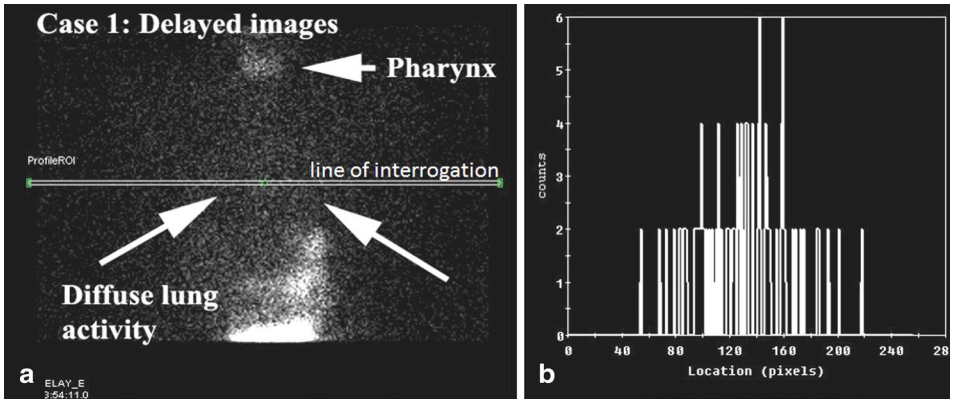


Fig. 17 Scintigraphy. **a** Scintigraphic images of reflux and pulmonary aspiration. **b** Scintigraphic counts at line of interrogation

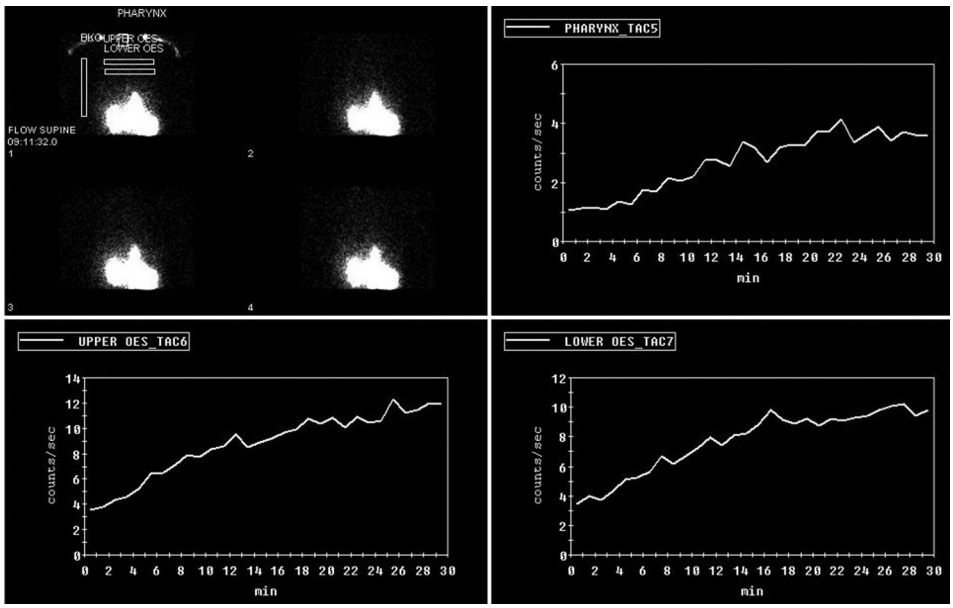


Fig. 18 Scintigraphy showing rising levels of pharyngeal contamination

Cough suppression

Short 3-day courses of prednisone 25 mg have occasionally given relief albeit transient, anecdotally. In a search of the literature (PubMed), dextromethorpan has shown no value, although it has been recommended [157]. Ketamine has not proven helpful [158]. Morphine and gabapentin have been symptomatically useful, but limited by dependence [159, 160].

Pain modulation

Treatment of patients with sensitive oesophagus and partial response to PPI may benefit from visceral pain management [107]. Other groups have also had a favourable experience with pain modulation in non-erosive reflux disease and LPR [161, 162].

Surgical treatment

Mainie et al. [163] report a group of surgical patients with selection by multichannel intraluminal impedance pH monitoring in a group of PPI unresponsive LPR symptoms. Patients with abnormal non-acid reflux were selected for antireflux surgery. Excellent results were obtained in a high proportion of patients. In contradistinction however, results of surgery have been generally disappointing, adequate results being reported in the 60 % range [60, 164–171]. We have reported a group of patients with good results for LPR symptoms with favourable results in excess of 90 % [80] similarly to the group of Mainie et al. [29] suggesting that adequate identification of pharyngeal reflux without recourse to acid detection may have value. It may be that accurate determination of reflux contamination proximally may allow a group of patients to be adequately selected for surgery. Multiple studies of surgical therapy while having less than uniform results have substantial response rates in 60–80 % of selected patients, with improvements in asthma control, reduction in cough and throat symptoms range [60, 164–171].

The difficulty remains, it seems; in selection of appropriate patient groups for surgery, rather than doubt about disease existence. Results obtained by our group are by multidisciplinary exclusion of alternative disease and a combination of standardised reflux scintigraphy and initially 2 channel 24-h pH study, later evolving to 2 channel impedance studies (proximal and distal). The gold standard accurate diagnostic test predictive of symptoms and therapeutic outcome, however, remains elusive. Medical treatment remains empirical, and evidence suggests there is a low prospect of amelioration of symptoms of LPR. Occasional patients seem to gain some symptom reduction.

Compliance with ethical standards

Conflict of interest
The authors declare no conflict of interest.

Appendix

Concord atypical reflux group

Prof. Gregory L. Falk—sydney.heartburn@gmail.com
Prof. Hans Van der Wall—hvanderwall@gmail.com
Ms. Leticia Burton—leticia.burton@gmail.com
Ms. SarahJayne Vivian—sarahjaynevivian@gmail.com
Dr. Arj Ananda—ananda@drananda.com.au
Dr. John Beattie—drjcbeattie@gmail.com
Prof. Alvin Ing—ajing@med.usyd.edu.au
Dr. Stephen Parsons—sparsons@bigpond.net.au

References

1. Perry KA, Pham TH, Spechler SJ, Hunter JG, Melvin WS, Velanovich V. 2014 SSAT State-of-the-Art Conference: advances in diagnosis and management of Gastroesophageal Reflux Disease. J Gastrointest Surg. 2015;19(3):458–66. http://link.springer.com/10.1007/s11605-014-2724-9.
2. Wong R. ENT manifestations of gastroesophageal reflux. Am J Gastroenterol. 2000;95(1):S15–22. http://linkinghub.elsevier.com/retrieve/pii/S0002927000010741.
3. Vaezi MF. Extraesophageal Reflux. San Diego: Plural Publishing; 2009.
4. Vakil N, van Zanten SV, Kahrilas P, Dent J, Jones R. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. Am J Gastroenterol. 2006;101(8):1900–20, quiz 1943. http://www.ncbi.nlm.nih.gov/pubmed/16928254 [cited 2014 Mar 26].
5. Gastroenterological Society of Australia. Gastro-oesophageal reflux disease in adults. 5. Edn. Mulgrave: Digestive Health Foundation; 2011.
6. Mittal RK, Holloway RH, Penagini R, Blakshaw LA, Dent J. Transient lower esophageal relaxation. Gastroenterology. 1995;109:601–10.
7. Kahrilas P, Dodds W, Hogan W. Effect of peristaltic dysfunction on esophageal volume clearance. Gastroenterology. 1988;94:73–80. http://ukpmc.ac.uk/abstract/MED/3335301 [cited 2013 Jan 8].
8. Patti MG, Goldberg HI, Arcerito M, Bortolasi L, Tong J, Way LW. Hiatal hernia size affects lower esophageal sphincter function, esophageal acid exposure, and the degree of mucosal injury. Am J Surg. 1996;171(1):182–6. http://www.ncbi.nlm.nih.gov/pubmed/8554137.
9. Weijenborg PW, Smout AJPM, Verseijden C, van Veen HA, Verheij J, de Jonge WJ, et al. Hypersensitivity to acid is associated with impaired esophageal mucosal integrity in patients with gastroesophageal reflux disease with and without esophagitis. AJP Gastrointest Liver Physiol. 2014;307(3):G323–9. http://ajpgi.physiology.org/cgi/doi/10.1152/ajpgi.00345.2013.
10. Björkman EVC, Edebo A, Oltean M, Casselbrant A. Esophageal barrier function and tight junction expression in healthy subjects and patients with gastroesophageal reflux disease: functionality of esophageal mucosa exposed to bile salt and trypsin in vitro. Scand J Gastroenterol. 2013;48(10):1118–26. http://www.tandfonline.com/doi/full/10.3109/00365521.2013.828772.
11. Mönkemüller K, Wex T, Kuester D, Fry LC, Kandulski A, Kropf S, et al. Role of tight junction proteins in gastroesophageal reflux disease. BMC Gastroenterol. 2012;12(1):128. http://www.biomedcentral.com/1471-230X/12/128.
12. Hyun JJ, Bak Y-T. Clinical Significance of Hiatal Hernia. Gut Liver. 2011;5(3):267–77.
13. Sloan S, Rademaker AW, Kahrilas PJ. Determinants of Gastroesophageal Junction Incompetence: hiatal Hernia, Lower Esophageal Sphincter, or Both? Ann Intern Med 1992;117(12):977. http://annals.org/article.aspx?doi=10.7326/0003-4819-117-12-977.
14. Kahrilas PJ, Lin S, Chen J, Manka M. The effect of hiatus hernia on gastro-oesophageal junction pressure. Gut. 1999;44(4):476–82.
15. Behar J, Sheahan D. Histologic abnormalities in reflux esophagitis. Arch Pathol. 1975;99(7):387–91.
16. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med. 1999;340(11):825–31.
17. Poh CH, Gasiorowska A, Navarro-Rodriguez T, Willis MR, Hargadon D, Noelck N, et al. Upper GI tract findings in patients with heartburn in whom proton pump inhibitor treatment failed versus those not receiving antireflux treatment. Gastrointest Endosc. 2010;71(1):28–34. http://linkinghub.elsevier.com/retrieve/pii/S0016510709024249.
18. Dent J, Vakil N, Jones R, Bytzer P, Schöning U, Halling K, et al. Accuracy of the diagnosis of GORD by questionnaire, physicians and a trial of proton pump inhibitor treatment: the Diamond Study. Gut. 2010 [cited 2013 Nov 6];59(6):714–21. http://www.ncbi.nlm.nih.gov/pubmed/20551454.
19. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. Nature Publishing Group; 2013;108(3):308–28, quiz 329. http://www.ncbi.nlm.nih.gov/pubmed/23419381. Accessed 2013 May 22
20. Pera M, Cameron AJ, Trastek VF, Carpenter HA, Zinsmeister AR. Increasing incidence of adenocarcinoma of the esophagus and esophagogastric junction. Gastroenterology. 1993;104(2):510–3.
21. Di Pietro M, Fitzgerald RC. Screening and risk stratification for Barrett's Esophagus. How to limit the clinical impact of the increasing incidence of Esophageal Adenocarcinoma. Gastroenterol Clin North Am. 2013;42(1):155–73.

22. Haidry RJ, Dunn JM, Butt MA, Burnell M, Gupta A, Green S, et al. Radiofrequency Ablation (Rfa) And Endoscopic Mucosal Resection For Dysplastic Barrett's Esophagus And Early Esophageal Adenocarcinoma: Outcomes Of Uk National Halo Rfa Registry. Gastroenterology. AGA Institute American Gastroenterological Association; 2013;(April):3447. http://www.ncbi.nlm.nih.gov/pubmed/23542069. Accessed 2013 Apr 4
23. Shaheen N, Sharma P, Overholt B, Radiofrequency ablation in Barrett's esophagus with dysplasia. Engl J. 2009;360(22):2277–88. http://www.nejm.org/doi/full/10.1056/NEJMoa0808145. Accessed 2012 Jul 12
24. Fleischer DE, Odze R, Overholt BF, Carroll J, Chang KJ, Das A, et al. The case for Endoscopic treatment of non-dysplastic and low-grade Dysplastic Barrett's Esophagus. Dig Dis Sci. 2010;55(7):1918–31. http://www.ncbi.nlm.nih.gov/pubmed/20405211. Accessed 2012 Jul 12
25. Kristo I, Schoppmann SF, Riegler M, Püspök A, Emmanuel K, Spaun G, et al. Austrian expert panel recommendation for radiofrequency ablation of Barrett's esophagus. Eur Surg. 2015;47(6):319–23. http://link.springer.com/10.1007/s10353-015-0362-4.
26. Evans JA, Early DS, Fukami N, Ben-Menachem T, Chandrasekhara V, Chathadi KV, et al. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. Gastrointest Endosc 2012;76(6):1087–94. http://linkinghub.elsevier.com/retrieve/pii/S0016510712025746.
27. National Institute for Health and Care Excellence. Endoscopic radiofrequency ablation for Barrett ' s oesophagus with low-grade dysplasia or no dysplasia 2014. www.guidance.nice.org.uk/ipg496.
28. Johnson L, Demeester T. Twenty-four-hour pH monitoring of the distal esophagus. A quantitative measure of gastroesophageal reflux. Am J Gastroenterol 1974;62:325–32. http://europepmc.org/abstract/med/4432845. Accessed 2015 Mar 20
29. Mainie I, Tutuian R, Shay S, Vela M, Zhang X, Sifrim D, et al. Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. Gut. 2006;55(10):1398–402.
30. Gyawali CP. High resolution manometry: the ray clouse legacy. Neurogastroenterol Motil. 2012;24(SUPPL 1):2–4.
31. Pandolfino JE, Richter JE, Ours T, Guardino JM, Chapman J, Kahrilas PJ. Ambulatory esophageal pH monitoring using a wireless system. Am J Gastroenterol. 2003;98(4):740–9. http://www.ncbi.nlm.nih.gov/pubmed/12738450.
32. Lundell LR, Dent J, Bennett JR, Blum a L, Armstrong D, Galmiche JP, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999;45(2):172–80.
33. Sifrim D, Zerbib F. Diagnosis and management of patients with reflux symptoms refractory to proton pump inhibitors. Gut. 2012;61(9):1340–54. http://www.ncbi.nlm.nih.gov/pubmed/22684483. Acessed 2013 Feb 4
34. Labenz J, Armstrong D, Lauritsen K, Katelaris P, Schmidt S, Schütze K, et al. A randomized comparative study of esomeprazole 40 mg versus pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. Aliment Pharmacol Ther. 2005;21(6):739–46. http://www.ncbi.nlm.nih.gov/pubmed/15771760.
35. Castell DO, Kahrilas PJ, Richter JE, Vakil NB, Johnson DA, Zuckerman S, et al. Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol. 2002;97(3):575–83. http://www.ncbi.nlm.nih.gov/pubmed/11922549\nhttp://www.nature.com/ajg/journal/v97/n3/pdf/ajg2002150a.pdf.
36. Zerbib F, Sifrim D, Tutuian R, Attwood S, Lundell L. Modern medical and surgical management of difficult-to-treat GORD., United Eur Gastroenterol J. 2013;1(1):21–31. http://ueg.sagepub.com/lookup/doi/10.1177/2050640612473964.
37. Shah NH, LePendu P, Bauer-Mehren A, Ghebremariam YT, Iyer SV, Marcus J, et al. Proton pump inhibitor usage and the risk of myocardial infarction in the general population. PLoS One. 2015;10(6):e0124653. http://dx.plos.org/10.1371/journal.pone.0124653.
38. SAGES. Guidelines for Surgical Treatment of Gastroesophageal Reflux Disease (GERD) Limitations of the Available Literature. 2001. p. 1–22.
39. Jobe BA, Richter JE, Hoppo T, Peters JH, Bell R, Dengler WC, et al. Preoperative diagnostic workup before antireflux surgery: an evidence and experience-based consensus of the esophageal diagnostic advisory panel. J Am Coll Surg 2013;217(4):586–97. http://linkinghub.elsevier.com/retrieve/pii/S1072751513004249.
40. Attwood SE, Lundell L, Ell C, Galmiche J-P, Hatlebakk J, Fiocca R, et al. Standardization of surgical technique in antireflux surgery: the LOTUS Trial experience. World J Surg. 2008;32(6):995–8. http://www.ncbi.nlm.nih.gov/pubmed/18224465. Accessed 2014 Dec 1
41. Nissen R. [A simple operation for control of reflux esophagitis]. Schweiz Med Wochenschr. 1956;86(Suppl 20):590–2. http://www.ncbi.nlm.nih.gov/pubmed/13337262.
42. Kristo I, Schoppmann SF. Diagnosis and treatment of benign inflammatory esophageal diseases. Eur Surg. 2015;47(4):188–98. http://link.springer.com/10.1007/s10353-015-0329-5.
43. DelGaudio JM. Direct nasopharyngeal reflux of gastric acid is a contributing factor in refractory chronic rhinosinusitis. Laryngoscope. 2005;115(6):946–57. http://www.ncbi.nlm.nih.gov/pubmed/15933499.
44. Barbero GJ. Gastroesophageal reflux and upper airway disease. Otolaryngol Clin North Am. 1996;29(1):27–38. http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&DbFrom=pubmed&Cmd=Link&LinkName=pubmed_pubmed&LinkReadableName=RelatedArticles & IdsFromResult=8834270&ordinalpos=3&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum\nhttp://www.ncbi.n.
45. Meurman JH, Toskala J, Nuutinen P, Klemetti E. Oral and dental manifestations in gastroesophageal reflux disease. Oral Surg Oral Med Oral Pathol. 1994;78(5):583–9. http://www.ncbi.nlm.nih.gov/pubmed/7838463.
46. Moazzez R, Bartlett D, Anggiansah A. Dental erosion, gastro-oesophageal reflux disease and saliva: how are they related? J Dent. 2004;32(6):489–94.
47. Järvinen V, Meurman JH, Hyvärinen H, Rytömaa I, Murtomaa H. Dental erosion and upper gastrointestinal disorders. Oral Surgery. Oral Med Oral Pathol. 1988;65(3):298–303.
48. Oginni AO, Agbakwuru EA, Ndububa DA. The prevalence of dental erosion in Nigerian patients with gastro-oesophageal reflux disease. BMC Oral Health. 2005;5(1):1. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=554987&tool=pmcentrez&rendertype=abstract.

49. Muñoz JV, Herreros B, Sanchiz V, Amoros C, Hernandez V, Pascual I, et al. Dental and periodontal lesions in patients with gastro-oesophageal reflux disease. Dig Liver Dis. 2003;35(7):461–7. http://www.ncbi.nlm.nih.gov/pubmed/12870730.
50. Stovold R, Forrest IA, Corris PA, Murphy DM, Smith J, Decalmer S, et al. Pepsin, a biomarker of gastric aspiration in lung allografts: a putative association with rejection. Am J Respir Crit Care Med. 2007;175(12):1298–303. http://www.ncbi.nlm.nih.gov/pubmed/17413126.
51. Hartwig MG, Appel JZ, Duane Davis R. Antireflux surgery in the setting of lung transplantation: strategies for treating gastroesophageal reflux disease in a high-risk population. Thorac Surg Clin. 2005;15(3):417–27. http://linkinghub.elsevier.com/retrieve/pii/S1547412705000150.
52. Cantu E, Appel JZ, Hartwig MG, Woreta H, Green C, Messier R, et al. Early fundoplication prevents chronic allograft dysfunction in patients with gastroesophageal reflux disease. Ann Thorac Surg. 2004;78(4):1142–51. http://linkinghub.elsevier.com/retrieve/pii/S0003497504009725.
53. O'Halloran EK, Reynolds JD, Lau CL, Manson RJ, Davis RD, Palmer SM, et al. Laparoscopic Nissen fundoplication for treating reflux in lung transplant recipients. J Gastrointest Surg. 2004;8(1):132–7. http://www.ncbi.nlm.nih.gov/pubmed/14746846.
54. Davis CS, Shankaran V, Kovacs EJ, Gagermeier J, Dilling D, Alex CG, et al. Gastroesophageal reflux disease after lung transplantation: pathophysiology and implications for treatment. Surgery 2010;148(4):737–45. http://linkinghub.elsevier.com/retrieve/pii/S0039606010003739.
55. Irwin RS. Chronic Cough Due to Gastroesophageal Reflux Disease: ACCP Evidence-Based Clinical Practice Guidelines. Chest. 2006;129(1_suppl):80S–94S.
56. Ing A, Ngu M. Chronic persistent cough and gastro-oesophageal reflux Thorax. Concord; 1995. http://thorax.bmj.com/content/46/7/479.abstract.
57. Ing a J, Ngu MC. Cough and gastro-oesophageal reflux. Lancet. 1999;353(9157):944–6. http://www.ncbi.nlm.nih.gov/pubmed/10459900.
58. Smith JA, Houghton LA. The oesophagus and cough: laryngo-pharyngeal reflux, microaspiration and vagal reflexes. Cough. 2013;9(1):12. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3640905&tool=pmcentrez&rendertype=abstract.
59. Hu X, Lee JS, Pianosi PT, Ryu JH, Aspiration-Related Pulmonary Syndromes. Chest J. 2015;147(3):815. http://www.ncbi.nlm.nih.gov/pubmed/25732447. Accessed 2015 Mar 20
60. Ekström T, Johansson KE. Effects of anti-reflux surgery on chronic cough and asthma in patients with gastro-oesophageal reflux disease. Respir Med. 2000;94(12):1166–70.
61. Komatsu Y, Hoppo T, Jobe B. Proximal reflux as a cause of adult-onset Asthma. JAMA Surg. 2013;148(1):50–8. http://scholar.google.com/scholar?hl=en&btnG=Search&q=intitle:Proximal+Reflux+as+a+Cause+of+Adult-Onset+Asthma#3. Accessed 2014 Feb 26
62. Madanick RD. Extraesophageal presentations of GERD: where is the science? Gastroenterol Clin North Am. 2014;43(1):105–20. http://www.ncbi.nlm.nih.gov/pubmed/24503362. Accessed 2014 Dec 1
63. Hoppo T, Jarido V, Pennathur A, Morrell M, Crespo M, Shigemura N, et al. Antireflux surgery preserves lung function in patients with gastroesophageal reflux disease and end-stage lung disease before and after lung transplantation. Arch Surg. 2011;146(9):1041–7. http://www.ncbi.nlm.nih.gov/pubmed/21931001.
64. He Z, O'Reilly R, Bolling L, Soundar S, Shah M, Cook S, et al. Detection of gastric pepsin in middle ear fluid of children with otitis media. Otolaryngol - Head Neck Surg. 2007 137(1):59–64. http://oto.sagepub.com/lookup/doi/10.1016/j.otohns.2007.02.002.
65. Qadeer MA, Colabianchi N, Strome M, Vaezi MF. Gastroesophageal reflux and laryngeal cancer: causation or association? A critical review. Am J Otolaryngol. 2006;27(2):119–28. http://linkinghub.elsevier.com/retrieve/pii/S0196070905001390.
66. Ludemann JP, Manoukian J, Shaw K, Bernard C, Davis M, Al-Jubab A. Effects of simulated gastroesophageal reflux on the untraumatized rabbit larynx. J Otolaryngol. 1998;27(3):127–31.
67. Johnston N, Dettmar PW, Bishwokarma B, Lively MO, Koufman JA. Activity/stability of human pepsin: implications for reflux attributed laryngeal disease. Laryngoscope. 2007;117:1036–9.
68. Johnston N, Wells CW, Blumin JH, Toohill RJ, Merati AL. Receptor-mediated uptake of pepsin by laryngeal epithelial cells. Ann Otol Rhinol Laryngol. 2007;116(12):934–8. http://www.ncbi.nlm.nih.gov/pubmed/18217514.
69. Ing A, Ngu M, Breslin A. Chronic persistent cough and clearance of esophageal acid. Chest. 1992;102:1668–71. http://chestjournal.chestpubs.org/content/102/6/1668.short. Accessed 2013 Jan 8
70. Fornari F, Blondeau K, Durand L, Rey E, Diaz-Rubio M, De Meyer A, et al. Relevance of mild ineffective oesophageal motility (IOM) and potential pharmacological reversibility of severe IOM in patients with gastro-oesophageal reflux disease. Aliment Pharmacol Ther. 2007;26(10):1345–54.
71. Simrén M, Silny J, Holloway R, Tack J, Janssens J, Sifrim D. Relevance of ineffective oesophageal motility during oesophageal acid clearance. Intergovernmental panel on climate change. editor. Gut. Cambridge: Cambridge University Press; 2003;52(6):pp. 784–90.
72. Chen CL, Szczesniak MM, Cook IJ. Identification of impaired oesophageal bolus transit and clearance by secondary peristalsis in patients with non-obstructive dysphagia. Neurogastroenterol Motil. 2008;20(9):980–8.
73. Knight RE, Wells JR, Parrish RS. Esophageal dysmotility as an Important co-factor in extraesophageal manifestations of Gastroesophageal Reflux. Laryngoscope. 2000;110(9):1462–6. http://doi.wiley.com/10.1097/00005537-200009000-00010.
74. Fouad YM, Katz PO, Hatlebakk JG, Castell DO. Ineffective esophageal motility: the most common motility abnormality in patients with GERD-associated respiratory symptoms. Am J Gastroenterol. 1999;94(6):1464–7. http://www.ncbi.nlm.nih.gov/pubmed/10364008.
75. Kastelik JA, Redington a E, Aziz I, Buckton GK, Smith CM, Dakkak M, et al. Abnormal oesophageal motility in patients with chronic cough. Thorax. 2003;58(8):699–702. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1746758&tool=pmcentrez&rendertype=abstract.
76. Falk GL, Beattie J, Burton L, O'Donnell H, Falk MG, Van der Wall H, et al. Laryngopharyngeal reflux disease: correlation of reflux scintigraphy and 24 h impedance pH in a cohort of refractory symptomatic patients. Unpubl Work. 2015.
77. Ing A, Ngu M, Breslin A. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. Am J Respir Crit Care Med. 1994;149:160–7. http://ajrccm.atsjournals.org/content/149/1/160.short. Accessed 2013 Jan 8.

78. Javorkova N, Varechova S, Pecova R, Tatar M, Balaz D, Demeter M, et al. Acidification of the oesophagus acutely increases the cough sensitivity in patients with gastro-oesophageal reflux and chronic cough. Neurogastroenterol Motil. 2007;20(2):119–24. http://www.ncbi.nlm.nih.gov/pubmed/17999650. (071114170920003—???)
79. Collier BD. Detection of aspiration: scintigraphic techniques. Am J Med. 1997;103(5A):135S–137S. http://www.ncbi.nlm.nih.gov/pubmed/9422639.
80. Falk GL, Beattie J, Ing A, Falk SE, Magee M, Burton L, et al. Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? World J Gastroenterol. 2015;21(12):3619. http://www.wjgnet.com/1007–9327/full/v21/i12/3619.htm.
81. Morice AH, Fontana GA, Sovijarvi ARA, Pistolesi M, Chung KF, Widdicombe J, et al. The diagnosis and management of chronic cough. Eur Respir J. 2004. p. 481–92.
82. Irwin R, French C, Curley F, Zawacki J, Bennett F. Chronic cough due to gastroesophageal reflux. Clinical, diagnostic, and pathogenetic aspects. Chest. 1993;104(5):1511–7.
83. Pratter MR. Overview of Common Causes of Chronic Cough. Chest. 2006;129(1 Suppl):59S–62S.
84. Qiu ZZ, Yu L, Xu S, Liu B, Zhao T, Lü H, et al. Cough reflex sensitivity and airway inflammation in patients with chronic cough due to non-acid gastro-oesophageal reflux. Respirology. 2011;16(4):645–52. http://www.ncbi.nlm.nih.gov/pubmed/21342332. Accessed 2012 Dec 13.
85. Ziora D, Jarosz W, Dzielicki J, Ciekalski J, Krzywiecki A, Dworniczak S, et al. Citric acid cough threshold in patients with gastroesophageal reflux disease rises after laparoscopic fundoplication. Chest. 2005;2458–64.
86. Falk GL, Beattie J. Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? World J Gastroenterol. 2015;21(12):3619. http://www.wjgnet.com/1007–9327/full/v21/i12/3619.htm.
87. Spechler S. Laryngopharyngeal reflux: a cause of faulty phonation or a faulted, phony diagnosis? Clin Gastroenterol Hepatol. 2006;4(4):431–2. http://www.cghjournal.org/article/S1542-3565(06)00079 – 6/abstract. Accessed 2013 Jan 8.
88. Navaratnam RM, Winslet MC. Gastro-oesophageal reflux: the disease of the millennium. Hosp Med. 1998;59(8):646–9. http://www.ncbi.nlm.nih.gov/pubmed/9829061.
89. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice. 2002;16(2):274–7.
90. Habermann W, Schmid C, Neumann K, Devaney T, Hammer HF. Reflux symptom index and reflux finding score in otolaryngologic practice. J Voice. 2012;26(3):e123–7. http://dx.doi.org/10.1016/j.jvoice.2011.02.004.
91. Ahmed TF, Khandwala F, Abelson TI, Hicks DM, Richter JE, Milstein C, et al. Chronic laryngitis associated with gastroesophageal reflux: prospective assessment of differences in practice patterns between gastroenterologists and ENT physicians. Am J Gastroenterol. 2006;101(3):470–8. http://www.ncbi.nlm.nih.gov/pubmed/16542282.
92. Branski RC, Bhattacharyya N, Shapiro J. The reliability of the assessment of endoscopic laryngeal findings associated with laryngopharyngeal reflux disease. Laryngoscope. 2002;112(6):1019–24.
93. Hicks DM, Ours TM, Abelson TI, Vaezi MF, Richter JE. The prevalence of hypopharynx findings associated with Gastroesophageal Reflux in normal volunteers. J Voice. 2002;16(4):564–79. http://linkinghub.elsevier.com/retrieve/pii/S0892199702001327.
94. Milstein CF, Charbel S, Hicks DM, Abelson TI, Richter JE, Vaezi MF. Prevalence of laryngeal irritation signs associated with reflux in asymptomatic volunteers: impact of Endoscopic Technique (Rigid vs. Flexible Laryngoscope). Laryngoscope. 2005;115(12):2256–61. http://doi.wiley.com/10.1097/01.mlg.0000184325.44968.b1.
95. Kelchner LN, Horne J, Lee L, Klaben B, Stemple JC, Adam S, et al. Reliability of speech-language pathologist and otolaryngologist ratings of laryngeal signs of reflux in an asymptomatic population using the reflux finding score. J Voice. 2007;21(1):92–100. http://www.ncbi.nlm.nih.gov/pubmed/16546351.
96. Musser J, Kelchner L, Neils-Strunjas J, Montrose M. A comparison of rating scales used in the diagnosis of extraesophageal reflux. J Voice. 2011;25(3):293–300. http://www.ncbi.nlm.nih.gov/pubmed/20202786.
97. de Bortoli N, Nacci A, Savarino E, Martinucci I, Bellini M, Fattori B, et al. How many cases of laryngopharyngeal reflux suspected by laryngoscopy are gastroesophageal reflux disease-related? World J Gastroenterol. 2012;18(32):4363–70.
98. Vavricka SR, Storck CA, Wildi SM, Tutuian R, Wiegand N, Rousson V, et al. Limited diagnostic value of laryngopharyngeal lesions in patients with gastroesophageal reflux during routine upper gastrointestinal endoscopy. Am J Gastroenterol. 2007;102(4):716–22.
99. Belafsky PC, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). Laryngoscope. 2001;111(8):1313–7.
100. Garnett JD. Contact Granulomas. Medscape. 2015. http://emedicine.medscape.com/article/865924-overview.
101. Vaezi MF, Hicks DM, Abelson TI, Richter JE. Laryngeal signs and symptoms and gastroesophageal reflux disease (GERD): a critical assessment of cause and effect association. Clin Gastroenterol Hepatol. 2003;1(5):333–44.
102. Koufman JA. The Otolaryngologic Manifestations of Gastroesophageal Reflux Disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal. Laryngoscope. 1991;101:1–77.
103. Sifrim D, Dupont L, Blondeau K, Zhang X, Tack J, Janssens J. Weakly acidic reflux in patients with chronic unexplained cough during 24 h pressure, pH, and impedance monitoring. Gut. 2005;54(4):449–54. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1774432&tool=pmcentrez&rendertype=abstract. Accessed 2015 Jan 2.
104. Zerbib F, Stoll D. Management of laryngopharyngeal reflux: an unmet medical need. Neurogastroenterol Motil. 2010;22(2):109–12.
105. Ciecierega T, Gordon BL, Aronova A, Crawford CV, Zarnegar R. More Art than Science: impedance analysis prone to interpretation error. J Gastrointest Surg. 2015;19(6):987–92. http://link.springer.com/10.1007/s11605-015-2809-0.
106. Zhou LY, Wang Y, Lu JJ, Lin L, Cui RL, Zhang HJ, et al. Accuracy of diagnosing gastroesophageal reflux disease by GerdQ, esophageal impedance monitoring and histology. J Dig Dis. 2014;15(5):230–8. http://www.ncbi.nlm.nih.gov/pubmed/24528678.
107. Zerbib F, Roman S, Bruley Des Varannes S, Gourcerol G, Coffin B, Ropert A, et al. Normal Values of Pharyngeal and Esophageal 24-Hour pH Impedance in individuals on and off therapy and interobserver reproducibility. Clin Gastroenterol Hepatol. 2013;11(4):366–72. http://linkinghub.elsevier.com/retrieve/pii/S1542356512013092?showall=true. (W.B. Saunders for the American Gastroenterological Association)

108. Hopkins C, Yousaf U, Pedersen M. Acid reflux treatment for hoarseness Cochrane Database Syst Rev. 2006. http://www.ncbi.nlm.nih.gov/pubmed/16437513.
109. Martinucci I, de Bortoli N, Savarino E, Nacci A, Romeo SO, Bellini M, et al. Optimal treatment of laryngopharyngeal reflux disease. Ther Adv Chronic Dis. 2013;4(6):287–301. http://taj.sagepub.com/cgi/doi/10.1177/2040622313503485.
110. Karkos PD, Wilson JA. Empiric treatment of laryngopharyngeal reflux with proton pump inhibitors: a systematic review. Laryngoscope. 2006;116:144–8.
111. Qadeer MA, Phillips CO, Lopez AR, Steward DL, Noordzij JP, Wo JM, et al. Proton pump inhibitor therapy for suspected GERD-related chronic laryngitis: a meta-analysis of randomized controlled trials. Am J Gastroenterol. 2006;101(11):2646–54.
112. Asaoka D, Nagahara A, Matsumoto K, Hojo M, Watanabe S. Current perspectives on reflux laryngitis. Clin J Gastroenterol. 2014;7(6):471–5. http://link.springer.com/10.1007/s12328-014-0535-x.
113. Tasker A, Dettmar PW, Panetti M, Koufman JA, P Birchall J, Pearson JP. Is gastric reflux a cause of otitis media with effusion in children? Laryngoscope. 2002;112(11):1930–4. http://www.ncbi.nlm.nih.gov/pubmed/12439157.
114. Lieu J, Muthappan P, Uppaluri R. Association of Reflux With Otitis Media in Children. Otolaryngol - Head Neck Surg. 2005;133(3):357–61. http://oto.sagepub.com/lookup/doi/10.1016/j.otohns.2005.05.654.
115. Tasker A, Dettmar PW, Panetti M, Koufman JA, Birchall JP, Pearson JP. Reflux of gastric juice and glue ear in children. Lancet. 2002;359(9305):493. http://www.ncbi.nlm.nih.gov/pubmed/11853797.
116. Dogru M, Kuran G, Haytoglu S, Dengiz R, Arikan OK, Role of Laryngopharyngeal Reflux in the Pathogenesis of Otitis Media with Effusion. J Int Adv Otol. 2015;11(1):66–71. http://www.advancedotology.org/eng/makale/823/87/Full-Text.
117. Decalmer S, Stovold R, Houghton LA, Pearson J, Ward C, Kelsall A, et al. Chronic cough: relationship between microaspiration, gastroesophageal reflux, and cough frequency. Chest. 2012;142(4):958–64.
118. Grabowski M, Kasran A, Seys S, Pauwels A, Medrala W, Dupont L, et al. Pepsin and bile acids in induced sputum of chronic cough patients. Respir Med. 2011;105(8):1257–61. http://www.sciencedirect.com/science/article/pii/S0954611111001612.
119. Pauwels A. Bile acids in Sputum and increased airway inflammation in patients with Cystic Fibrosis. Chest J. 2012;141(6):1568. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=22135379.
120. Iqbal M, Batch AJ, Spychal RT, Cooper BT. Outcome of surgical fundoplication for extraesophageal (atypical) manifestations of gastroesophageal reflux disease in adults: a systematic review. J Laparoendosc Adv Surg Tech A. 2008;18(6):789–96. http://www.ncbi.nlm.nih.gov/pubmed/19105666. Accessed 2014 Jan 31.
121. Bardhan KD, Strugala V, Dettmar PW. Reflux Revisited: advancing the role of pepsin. Int J Otolaryngol. 2012;2012:1–13. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3216344&tool=pmcentrez&rendertype=abstract.
122. Samuels T, Johnston N. Pepsin as a marker of extraesophageal reflux. Ann Otol Rhinol Laryngo. 2010;119(3):203–8.
123. Noordzij JP, Khidr A, Desper E, Meek RB, Reibel JF, Levine PA. Correlation of pH probe-measured laryngopharyngeal reflux with symptoms and signs of reflux laryngitis. Laryngoscope. 2002;112(12):2192–5. http://www.ncbi.nlm.nih.gov/pubmed/12461340. Accessed 2015 Jan 2.
124. Vaezi M, Schroeder P, Richter J. Reproducibility of proximal probe pH parameters in 24-hour ambulatory esophageal pH monitoring. Am J Gastroenterol. 1997;92:825–9. http://europepmc.org/abstract/MED/9149194. Accessed 2015 Jan 4
125. Kawamura O, Aslam M, Rittmann T, Hofmann C, Shaker R. Physical and pH properties of gastroesophagopharyngeal refluxate: a 24-hour simultaneous ambulatory impedance and pH monitoring study. Am J Gastroenterol. 2004;99(6):1000–10. http://www.ncbi.nlm.nih.gov/pubmed/15180717. Accessed 2015 Jan 4.
126. Merati A, Lim H, Ulualp S, Toohill R. Meta-analysis of upper probe measurements in normal subjects and patients with laryngopharyngeal reflux. Ann Otol Rhinol Laryngol. 2005;114:177–82. http://w.annals.com/toc/auto_article_process.php?year=2005&page=177&id=14155&sn=0. Accessed 2015 Jan 2.
127. Sun G, Muddana S, Slaughter JC, Casey S, Hill E, Farrokhi F, et al. A new pH catheter for laryngopharyngeal reflux: normal values. Laryngoscope. 2009;119(8):1639–43. http://doi.wiley.com/10.1002/lary.20282.
128. Sasaki C, Marotta J, Hundal J, Chow J, Eisen R. Bile-induced laryngitis: is there a basis in evidence? Ann Otol Rhinol Laryngol. 2005;114:192–7.
129. Divi V, Benninger MS. Diagnosis and management of laryngopharyngeal reflux disease. Curr Opin Otolaryngol Head Neck Surg. 2006;14(3):124–7. http://www.ncbi.nlm.nih.gov/pubmed/16728886.
130. Vela MFMF, Camacho-Lobato L, Srinivasan R, Tutuian R, Katz PO, Castell DO. Simultaneous intraesophageal impedance and pH measurement of acid and nonacid gastroesophageal reflux: effect of omeprazole. Gastroenterology. 2001;120(7):1599–606. http://linkinghub.elsevier.com/retrieve/pii/S0016508501428782. Accessed 2013 Feb 5.
131. Saritas Yuksel E, Vaezi MF. New developments in extraesophageal reflux disease. Gastroenterol Hepatol (N Y). 2012;8(9):590–9. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3594960&tool=pmcentrez&rendertype=abstract.
132. Maurer AH, Parkman HP. Update on Gastrointestinal Scintigraphy. Semin Nucl Med. 2006;36(2):110–8. http://linkinghub.elsevier.com/retrieve/pii/S0001299805000723.
133. Kjellén G, Brudin L, Håkansson HO. Is scintigraphy of value in the diagnosis of gastrooesophageal reflux disease? Scand J Gastroenterol. 1991;26(4):425–30. http://www.ncbi.nlm.nih.gov/pubmed/2034995.
134. Russell C. Functional evaluation of the esophagus. In: Hill L, editor. The Esophagus Medical and surgical management. Philadelphia: WB Saunders; 1988. p. 45.
135. Shay SS, Abreu SH, Tsuchida A. Scintigraphy in gastroesophageal reflux disease: a comparison to endoscopy, LESp, and 24-h pH score, as well as to simultaneous pH monitoring. Am J Gastroenterol. 1992;87(9):1094–101. http://www.ncbi.nlm.nih.gov/pubmed/1519565.
136. Thomas EJ, Kumar R, Dasan JB, Kabra SK, Bal CS, Menon S, et al. Gastroesophageal reflux in asthmatic children not responding to asthma medication: a scintigraphic study in 126 patients with correlation between scintigraphic and clinical findings of reflux. Clin Imaging. 2003;27(5):333–6. http://www.ncbi.nlm.nih.gov/pubmed/12932685.

137. Ravelli AM. Pulmonary Aspiration Shown by Scintigraphy in Gastroesophageal Reflux-Related Respiratory Disease. Chest J. 2006;130(5):1520. http://journal.publications.chestnet.org/article.aspx?doi=10.1378/chest.130.5.1520.
138. Ruth M, Carlsson S, Månsson I, Bengtsson U, Sandberg N. Scintigraphic detection of gastro-pulmonary aspiration in patients with respiratory disorders. Clin Physiol. 1993;13(1):19–33. http://www.ncbi.nlm.nih.gov/pubmed/8382143.
139. Falk M, Van der Wall H, Falk GL. Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms. Nucl Med Commun. 2015;36(6):625–30. http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006231-900000000-99055. Accessed 2015 Mar 20
140. Bestetti A, Carola F, Carnevali-Ricci P, Sambataro G, Tarolo GL. 99mTc-sulfur colloid gastroesophageal scintigraphy with late lung imaging to evaluate patients with posterior laryngitis. J Nucl Med. 2000;41(10):1597–602. http://www.ncbi.nlm.nih.gov/pubmed/11037986.
141. Pearson J, Parikh S, Orlando R, Johnston N, Allen J, Tinling S, et al. Review article: reflux and its consequences - the laryngeal, pulmonary and oesophageal manifestations. Aliment Pharmacol Ther. 2011;33(Suppl 1):1–71. http://doi.wiley.com/10.1111/j.1365–2036.2011.04581.x.
142. Anderson JW, Jhaveri MA. Reductions in medications with substantial weight loss with behavioral intervention. Curr Clin Pharmacol. 2010;5(4):232–8.
143. Fraser-Moodie CA, Norton B, Gornall C, Magnago S, Weale a R, Holmes GK. Weight loss has an independent beneficial effect on symptoms of gastro-oesophageal reflux in patients who are overweight. Scand J Gastroenterol. 1999;34(4):337–40.
144. Reimer C, Bytzer P. Management of laryngopharyngeal reflux with proton pump inhibitors. Ther Clin Risk Manag. 2008;4(1):225–33.
145. Fackler WK, Ours TM, Vaezi MF, Richter JE. Long-term effect of H2RA therapy on nocturnal gastric acid breakthrough. Gastroenterology. 2002;122(3):625–32. http://linkinghub.elsevier.com/retrieve/pii/S0016508502694454\nhttp://www.ncbi.nlm.nih.gov/pubmed/11874994.
146. Ours TM, Keith Fackler W, Richter JE, Vaezi MF. Nocturnal acid breakthrough: clinical significance and correlation with esophageal acid exposure. Am J Gastroenterol. 2003;98(3):545–50.
147. Boeckxstaens GE, Beaumont H, Mertens V, Denison H, Ruth M, Adler J, et al. Effects of lesogaberan on reflux and lower esophageal sphincter function in patients with gastroesophageal reflux disease. Gastroenterology. 2010;139(2):409–17. http://www.ncbi.nlm.nih.gov/pubmed/20451523.
148. Cossentino MJ, Mann K, Armbruster SP, Lake JM, Maydonovitch C, Wong RKH. Randomised clinical trial: the effect of baclofen in patients with gastro-oesophageal reflux—a randomised prospective study. Aliment Pharmacol Ther. 2012;35:1036–44. http://www.ncbi.nlm.nih.gov/pubmed/22428773.
149. Ciccaglione AF, Marzio L. Effect of acute and chronic administration of the GABA B agonist baclofen on 24 h pH metry and symptoms in control subjects and in patients with gastro-oesophageal reflux disease. Gut. 2003;52(4):464–70. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1773602&tool=pmcentrez&rendertype=abstract.
150. Shaheen NJ, Denison H, Bjorck K, Karlsson M, Silberg DG. Efficacy and safety of lesogaberan in gastro-oesophageal reflux disease: a randomised controlled trial. Gut. 2013;62(9):1248–55. http://gut.bmj.com/cgi/doi/10.1136/gutjnl-2012-302737.
151. Kelsall A, Houghton LA, Jones H, Decalmer S, McGuinness K, Smith JA. A novel approach to studying the relationship between subjective and objective measures of cough. Chest. 2011;139(3):569–75. http://www.ncbi.nlm.nih.gov/pubmed/20864619.
152. Dicpinigaitis PV, Rauf K. Treatment of chronic, refractory cough with baclofen. Respiration. 1998;65(1):86–8.
153. Xu X. Successful resolution of refractory chronic cough induced by gastroesophageal reflux with treatment of baclofen. Chest J. 2012;142(4_MeetingAbstracts):16 A. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3500706&tool=pmcentrez&rendertype=abstract.
154. Lidums I, Lehmann A, Checklin H, Dent JHR. Control of transient lower esophageal sphincter relaxations and reflux by the GABA(B) agonist baclofen in normal subjects. Gastroenterology. 2000;118(1):7–13.
155. Dicpinigaitis P, Dobkin J, Rauf K, Aldrich T. Inhibition of capsaicin- induced cough by the gamma-aminobutyric acid agonist baclofen. J Clin Pharmacol. 1998;38:364–7.
156. Glicksman JT, Mick PT, Fung K, Carroll TL. Prokinetic agents and laryngopharyngeal reflux disease: prokinetic agents and laryngopharyngeal reflux disease: a systematic review. Laryngoscope. 2014;124(10):2375–9. http://doi.wiley.com/10.1002/lary.24738.
157. Pavesi L, Subburaj S, Porter-Shaw K. Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: a meta-analysis. Chest. 2001;120(4):1121–8.
158. Young E, Sumner H, Decalmer S, Houghton L, Woodcock A, Smith J. Does central up-regulation of the n-methyl-d-aspartate receptor contribute to cough reflex hypersensitivity? Am J Respir Crit Care Med. 2010;181(Meeting Abstracts):A5906.
159. Morice AH, Menon MS, Mulrennan SA, Everett CF, Wright C, Jackson J, et al. Opiate therapy in chronic cough. Am J Respir Crit Care Med. 2007;175(4):312–5. http://www.ncbi.nlm.nih.gov/pubmed/17122382.
160. Mintz S, Lee JK. Gabapentin in the treatment of intractable idiopathic chronic cough: case reports. Am J Med. 2006;119(5):e13–5. http://www.ncbi.nlm.nih.gov/pubmed/16651037.
161. Broekaert D, Fischler B, Sifrim D, Janssens J, Tack J. Influence of citalopram, a selective serotonin reuptake inhibitor, on oesophageal hypersensitivity: a double-blind, placebo-controlled study. Aliment Pharmacol Ther. 2006;23(3):365–70. http://www.ncbi.nlm.nih.gov/pubmed/16422995.
162. Viazis N, Keyoglou A, Kanellopoulos AK, Karamanolis G, Vlachogiannakos J, Triantafyllou K, et al. Selective Serotonin Reuptake inhibitors for the treatment of Hypersensitive Esophagus: A Randomized, Double-Blind, Placebo-Controlled Study. Am J Gastroenterol. 2012;107(11):1662–7. http://www.nature.com/doifinder/10.1038/ajg.2011.179.
163. Mainie I, Tutuian R, Agrawal A. Combined multichannel intraluminal impedance–pH monitoring to select patients with persistent gastro-oesophageal reflux for laparoscopic Nissen fundoplication. Br J Surg. 2006;93(12):1483–7. http://onlinelibrary.wiley.com/doi/10.1002/bjs.5493/full. Accessed 2015 Jan 5.

164. Novitsky YW, Zawacki JK, Irwin RS, French CT, Hussey VM, Callery MP. Chronic cough due to gastroesophageal reflux disease: efficacy of antireflux surgery. Surg Endosc. 2002;16(4):567–71. http://www.ncbi.nlm.nih.gov/pubmed/11972189. Accessed 2015 Jan 5.
165. Patti MG, Arcerito M, Tamburini A, Diener U, Feo CV, Safadi B, et al. Effect of laparoscopic fundoplication on gastroesophageal reflux disease-induced respiratory symptoms. J Gastrointest Surg. 1999;4(2):143–9. http://www.ncbi.nlm.nih.gov/pubmed/10675237.
166. Greason KL, Miller DL, Deschamps C, Allen MS, Nichols FC, Trastek VF, et al. Effects of antireflux procedures on respiratory symptoms. Ann Thorac Surg. 2002;73(2):381–5.
167. Brouwer R, Kiroff GK. Improvement of respiratory symptoms following laparoscopic Nissen fundoplication. ANZ J Surg. 2003;73(4):189–93.
168. Oelschlager BK, Eubanks TR, Oleynikov D, Pope C, Pellegrini CA. Symptomatic and physiologic outcomes after operative treatment for extraesophageal reflux. Surg Endosc. 2002;16(7):1032–6. http://www.ncbi.nlm.nih.gov/pubmed/11984664. Accessed 2013 Feb 27.
169. Spivak H, Smith CD, Phichith A, Galloway K, Waring JP, Hunter JG. Asthma and gastroesophageal reflux: fundoplication decreases need for systemic corticosteroids. J Gastrointest Surg. 1999;3(5):477–82.
170. Allen CJ, Anvari M. Gastro-oesophageal reflux related cough and its response to laparoscopic fundoplication. Thorax. 1998;53(11):963–8. http://thorax.bmj.com/cgi/doi/10.1136/thx.53.11.963.
171. Wright RC, Rhodes KP, Improvement of laryngopharyngeal reflux symptoms after laparoscopic Hill repair. Am J Surg. 2003;185(5):455–61. http://www.sciencedirect.com/science/article/pii/S0002961003000527. Accessed 2015 Jan 7.

Original article

Nuclear Medicine Communications

Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms

Michael Falk[a], Hans Van der Wall[b] and Gregory L. Falk[a]

Objectives **Gastro-oesophageal reflux disease (GERD) is poorly defined at best. Symptoms can be variable, ranging from none to heartburn, regurgitation and chest pain. When the reflux extends to the oropharynx [laryngopharyngeal reflux (LPR)], the symptoms can be protean and include cough and sore throat. We present the scintigraphic findings in two broad groups classified by symptoms as either GERD or LPR.**

Patients and methods **Patients with an established diagnosis of GERD or LPR by standard methods (95%) or high clinical pretest probability (5%) were scanned in the upright and supine position after swallowing ^{99m}Tc-DTPA. A delayed image was obtained at 2 h to evaluate the possibility of lung aspiration.**

Results **Studies were obtained in 285 patients (168 females, 117 males), with a mean age of 54 years. Of these, 80 had typical symptoms of GERD and 205 had LPR. The group with GERD had pharyngeal contamination in 49 and 14% showed pulmonary aspiration. The group with LPR had pharyngeal contamination in 65 and 23% had lung aspiration. Pharyngeal contamination was more common in the supine than in the upright position ($P = 0000$). Lung aspiration was correlated with upper oesophageal activity.**

Conclusion **Scintigraphic reflux studies are a good screening test for GERD and LPR as they can detect oropharyngeal reflux and lung aspiration in an unsuspected proportion of patients in both groups. The oropharynx and lung are sites that are out of reach of the current standards of investigation such as pH studies, manometry and impedance monitoring. *Nucl Med Commun* 36:625–630**

Nuclear Medicine Communications 2015, **36**:625–630

Keywords: cough, gastro-oesophageal reflux disease, laryngopharyngeal reflux, lung aspiration, oesophageal manometry, pH studies, scintigraphy

[a]Sydney Heartburn Clinic, Concord Hospital, University of Sydney, Macquarie University and [b]Concord Nuclear Imaging, Sydney, Australia

Correspondence to Hans Van der Wall, MBBS, PhD, Concord Nuclear Imaging, 4 Hospital Road, Concord West, Sydney, NSW 2138, Australia
Tel: +61 2 9736 1040; fax: +61 2 9736 2095; e-mail: hvanderwall@gmail.com

Received 4 September 2014 **Revised** 14 November 2014
Accepted 21 January 2015

Objectives

There is no clear-cut definition of gastro-oesophageal reflux disease (GERD). In 2006, the Montreal Consensus Group defined GERD as 'a condition which develops when the reflux of stomach contents causes troublesome symptoms or complications'. Symptoms include cough, sore throat, atypical chest pain and other apparent non-oesophageal symptoms. Heartburn and regurgitation are the two most common symptoms, with a small proportion of patients being asymptomatic [1,2]. GERD has a significantly different symptom profile to laryngopharyngeal reflux (LPR). LPR involves reflux of gastric contents that contaminate the larynx and pharynx, with the possibility of a reflex-mediated contribution. The major symptoms of pharyngeal inflammation may be nonspecific, presenting with chronic cough, hoarseness, throat clearing, sore throat, voice fatigue and a globus sensation.

The main problem with LPR, whether symptomatic or silent, is the risk of prolonged exposure leading to pulmonary disease secondary to lung aspiration. Symptoms may be nonspecific and suggestive of asthma, allergy, pulmonary disease, drugs and poor diagnostics [3]. There is, however, a vast array of nonspecific conditions that may be ascribed to GERD [4]. Not all chronic cough is because of LPR and the current methods of establishing LPR are flawed [5] as 50% of cases have no evidence of acid reflux on pH monitoring [6], and indirect laryngoscopy is unreliable [7].

We present data on scintigraphic studies in two distinct groups of patients with symptom profiles consistent with either proven GERD or LPR. These patients had undergone conventional manometry and 24 h pH monitoring that established the presence of GERD in both highly selected groups. The scintigraphic studies include the important assessment of tracer activity in the upper oesophagus or pharynx and lung aspiration.

Patients and methods

Population and clinical data

Patients were extracted from a research database of cases of either proven (95%) or with high clinical probability (5%) of GERD that had been approved by the Concord Hospital Ethics Committee. All patients were considered if they had symptoms typical of GERD (heartburn,

DOI: 10.1097/MNM.0000000000000289

chest pain) and abnormal oesophageal manometry or pH studies as described elsewhere [8]. Patients with predominantly upper respiratory tract symptoms who remained undiagnosed after 8 weeks of appropriate investigation were also included. The major upper respiratory tract symptoms were cough, sore throat, recurrent throat clearing, voice change, laryngospasm, aspiration, globus and regurgitation. A history of heartburn was also elicited. An experienced surgical consultant assessed the patients' histories and categorized them as having predominantly GERD or LPR symptoms.

Scintigraphy

Patients were fasted overnight and medications were ceased for the 24 h before the test. While upright, patients were positioned in front of a Hawkeye 4 gamma camera (General Electric, Milwaukee, Wisconsin, USA) with markers placed on the mandible and over the stomach to ensure that the regions of interest were within the field of view of the camera. Patients swallowed 100 ml of water with 40–60 MBq of ^{99m}Tc-DTPA, followed by another 50–100 ml of water to clear the mouth and oesophagus of radioactivity. Dynamic images of the pharynx, oesophagus and stomach were obtained for 5 min at 15 s/frame into a 64×64 matrix (Fig. 1). A second 30 min dynamic image was obtained in the supine position immediately following the upright study utilizing 30 s frames. Following acquisition of the supine study, the patients were given a further 50 ml of water with 60 MBq of ^{99m}Tc phytate (colloid), followed by 50 ml of water as a flush. Delayed images were obtained at 2 h to assess the presence of aspiration of tracer activity into the lungs. Images were analysed by time–activity curves over the pharynx, upper and lower half of the oesophagus and a background region over the right side of the chest (Fig. 2), away from the stomach and oesophagus. Delayed images were analysed by a line profile over the lungs (Figs 3 and 4). A line was scrolled down through the delayed image and the count profile was assessed for a significant spike in counts over the lung hilum and lower lobes. This was considered significant if the counts were at least twice the background activity. Different agents were used as DTPA clears rapidly from the stomach and oesophagus after reflux. The colloid will remain in the lungs if aspirated, unlike DTPA, which would be cleared from the lungs as in lung clearance studies. DTPA is also the major agent utilized in the extant literature for the initial stage of acquisition. The second dose of colloid increases the chance of detecting aspiration.

Results were recorded retrospectively in a database, showing refluxate detected over the upper oesophagus or pharynx on the erect and supine imaging, and whether aspirate was present in the lungs on delayed imaging.

Data analysis

Data were analysed using standard statistical methods as much of the analysis was of differences in the means by the two-tailed *t*-test by groups and variables. Pearson correlation coefficients (two tails) with significance levels of 0.05 were utilized when seeking correlations between the variables in each group of patients (GERD vs. LPR). Univariate and multivariate analyses were carried out to evaluate the possibility of variables predicting lung aspiration in the two groups. The Statistica V8 software (Statsoft, Tulsa, Oklahoma, USA) package was used for data analysis.

Results

Population and clinical data

There were 285 patients in total (168 females, 117 males), with a mean age of 54.4 years at scintigraphy (range 17–90 years). The group included 80 patients with symptoms suggestive of GERD (34 females, 46 males; mean age 48.9, range 17–83) and 205 patients with symptoms suggestive of LPR (134 females, 71 males; mean age 56.6, range 23–90). Symptom profiles are shown in Table 1.

Scintigraphy in the gastro-oesophageal reflux disease group

In this group of 80 patients, 22 (27.5%) refluxed tracer into the upper oesophagus on erect imaging (Fig. 1), and of these, 19 refluxed into the pharynx (23.75% of the total GERD population). On supine imaging, 41 patients (51.25%) refluxed tracer into the upper oesophagus, and of these, 39 into the pharynx (48.75% of the total GERD population). Eleven of these patients (13.75%) showed evidence of pulmonary aspiration on the delayed study (Fig. 4). These results are summarized in Table 2. No patient with an abnormal pH study was missed by the scintigraphic reflux study.

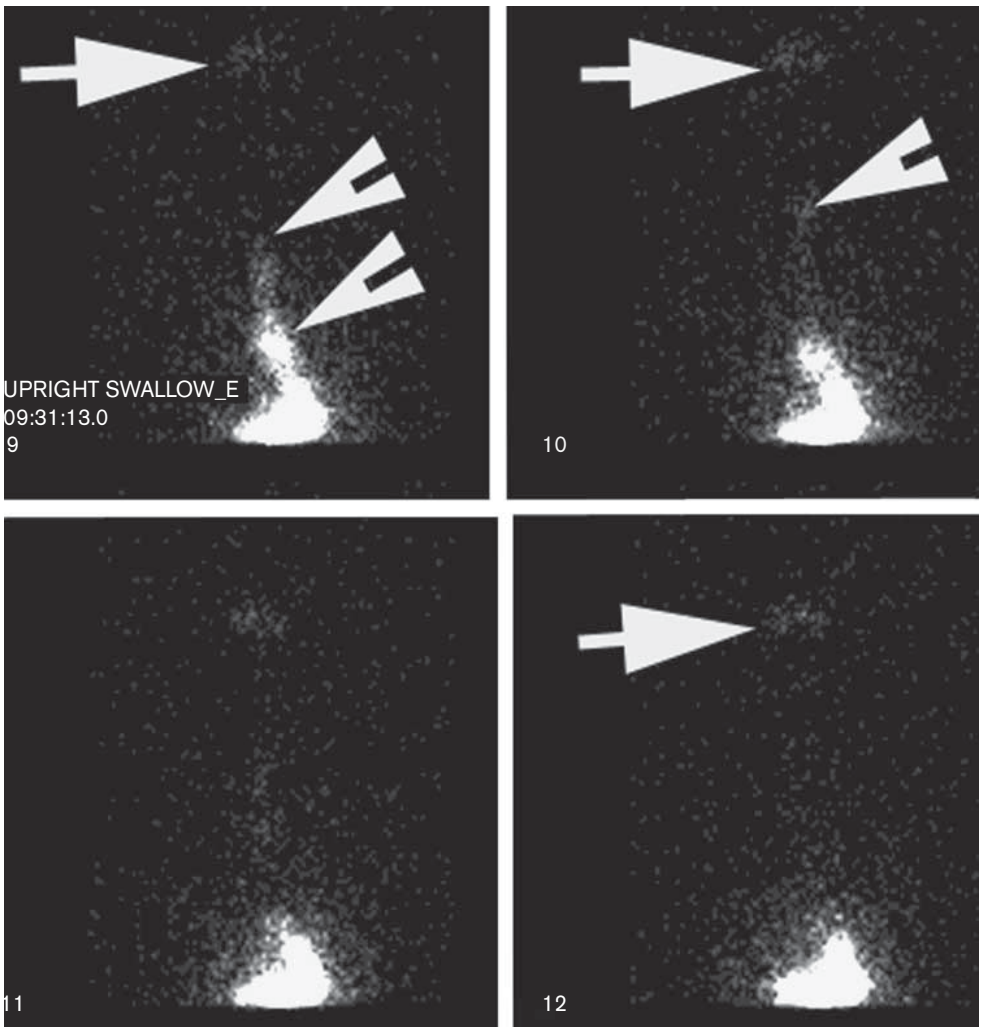
Scintigraphy in the laryngopharyngeal reflux group

In this group of 205 patients, 84 (40.98%) refluxed tracer into the upper oesophagus on the erect study (Fig. 1), and of these, 74 refluxed into the pharynx (36.1%). On supine imaging, 142 patients (69.27%) refluxed tracer into the upper oesophagus and of these, 133 refluxed into the pharynx (64.88%). Pulmonary aspiration was apparent in 48 patients (23.41%). These results are summarized in Table 3. No patient with an abnormal pH study was missed by the scintigraphic reflux study.

Statistical analysis

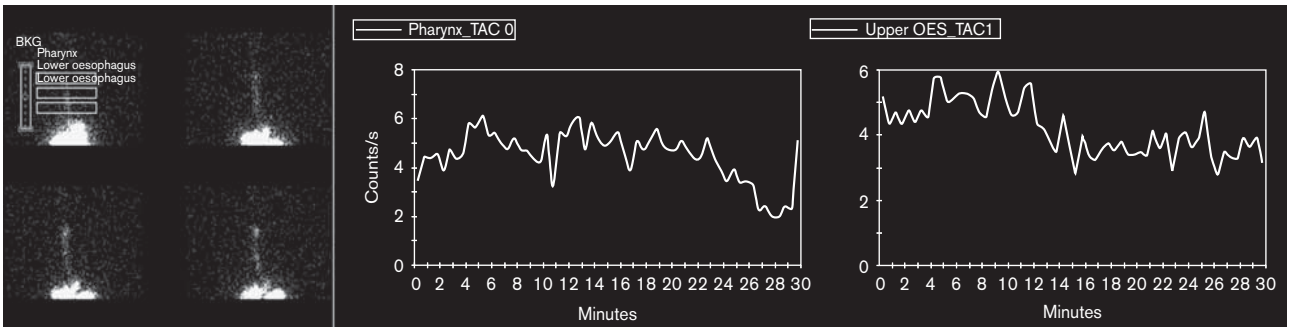
There was a significant difference between pharyngeal tracer activity in the upright and supine position for both the GERD and the LPR patients by the two-tailed *t*-test. For GERD patients, the difference was significant at a *P* value of 0.0005 ($t = 3.56$) and for the LPR patients, the difference was significant at a *P* value of 0.0000 ($t = 6.98$). A significant difference was also apparent between the supine GERD and LPR groups for pharyngeal activity, with a *P* value of 0.0084 ($t = 2.67$). Importantly, a significant difference was evident for the rates of lung

Fig. 1



Upright dynamic study. Four frames from the dynamic show full-column gastro-oesophageal reflux (arrowheads) with a progressive increase in activity in the oropharynx (arrow).

Fig. 2



Graphical analysis of activity in the upper oesophagus and oropharynx. The dynamic study in the first panel shows typical regions of interest over the pharynx, upper and lower oesophagus and background in a patient with full-column gastro-oesophageal reflux. The middle panel shows a progressive increase in activity over the pharynx with a similar initial pattern in the upper oesophagus.

aspiration in the GERD and LPR patients with a P value of 0.0026 ($t = 3.04$). There were correlations between lung aspiration, upper oesophageal upright ($P = 0.003$), upper oesophageal supine ($P = 0.029$) and pharyngeal upright ($P = 0.009$), but not pharyngeal supine ($P = 0.09$) in the GERD group. On multivariate analysis of the data

for the GERD patients, no variable was predictive of lung aspiration ($P > 0.05$). A good correlation was found between lung aspiration, upper oesophageal upright ($P = 0.000$), upper oesophageal supine ($P = 0.000$), pharyngeal upright ($P = 0.000$) and pharyngeal supine ($P = 0.006$) in the LPR group. In the LPR group, multivariate analysis found that upper oesophageal tracer activity in the supine position was predictive of lung aspiration of tracer ($P = 0.023$). Pharyngeal activity did not predict lung aspiration in either the upright or the supine position.

The power of the study for the evaluation of lung aspiration in the two groups of patients with GERD and

Table 1 Symptom profiles

GERD	Laryngopharyngeal reflux
Heartburn	Heartburn
Chest pain	Cough
	Sore throat
	Recurrent throat clearing
	Laryngospasm
	Voice change
	Aspiration
	Globus
	Regurgitation

GERD, gastro-oesophageal reflux disease.

Table 2 Presence of refluxate on reflux scintigraphy in patients with gastro-oesophageal reflux disease symptoms

GERD patients	$N = 80$ [n (%)]
Erect study	
Upper oesophagus	22 (27.50)
Pharynx	19 (23.75)
Supine study	
Upper oesophagus	41 (51.25)
Pharynx	39 (48.75)
Aspiration	11 (13.75)

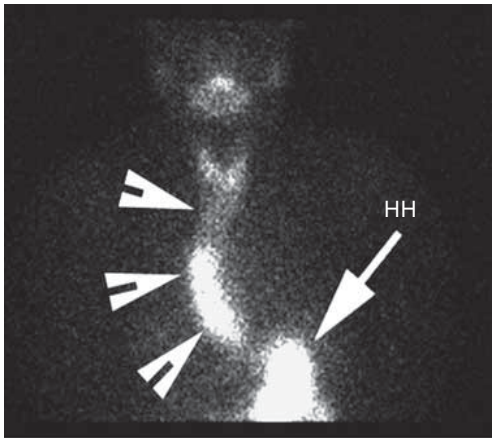
GERD, gastro-oesophageal reflux disease.

Table 3 Presence of refluxate on reflux scintigraphy in patients with LPR symptoms

LPR patients	$N = 205$ [n (%)]
Erect study	
Upper oesophagus	84 (40.98)
Pharynx	74 (36.10)
Supine study	
Upper oesophagus	142 (69.27)
Pharynx	133 (64.88)
Aspiration	48 (23.41)

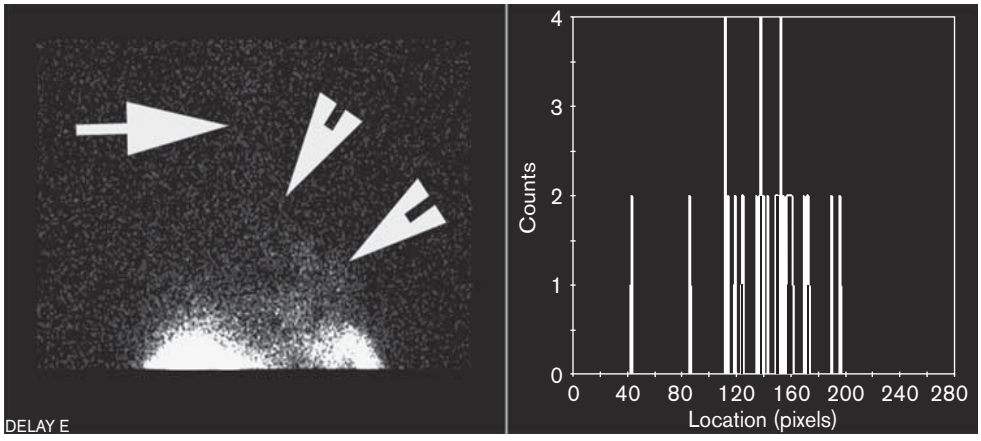
LPR, laryngopharyngeal reflux.

Fig. 3



The delayed study at 2 h shows persistent activity in the entire oesophagus (arrowheads) in a patient with a large hiatus hernia (HH, arrow). Uptake in the thyroid gland is also apparent from free pertechnetate in the colloid.

Fig. 4



Lung aspiration of tracer (arrowheads) in a patient with silent gastro-oesophageal reflux and established bronchiectasis. Note that there is no thyroid uptake in this case, indicating the absence of significant free pertechnetate that may have been taken up at the site of bronciectasis. Faint uptake is present in the oesophagus (arrow). The line profile on the right confirms persistent tracer activity in the oesophagus and at two sites in the left lower lobe (arrowheads).

LPR was 0.7, with an acceptable probability of type I or II errors.

Discussion

Traditional methods of a diagnosis for GERD have included endoscopy, pH monitoring and manometry, which provide a good assessment of the presence of acid reflux to the level of the upper oesophagus. Nonacid reflux is a major diagnostic issue [9], which has been addressed more recently by high-resolution manometry and impedance monitoring [10], which have shown promising results [11]. Impedance monitoring may also have the capacity to assess pharyngeal reflux, although reproducibility and reliability of the study may be an issue [11]. LPR poses a diagnostic problem as oropharyngeal reflux and lung aspiration are a relative blind spot for the established diagnostic techniques [12]. Scintigraphic reflux studies offer a valuable screening tool in the setting of suspected LPR (Figs 1 and 2) and may provide unexpected findings in the setting of GERD with silent LPR. Scintigraphy was applied in the setting of a highly selected group of patients with established diagnoses to evaluate its performance characteristics as a potential screening tool for pharyngeal reflux and lung aspiration.

Reflux scintigraphy is a simple and noninvasive technique. It shows direct contamination of the oropharynx and lungs by reflux disease (Figs 1 and 2). However, the technique requires strict standardization and attention to detail. Freshly prepared DTPA is a prerequisite to prevent free pertechnetate being taken up by the thyroid and salivary glands and interfering with the study. The volume of liquid in which the tracer is ingested and the framing rates are important if false-negative studies are to be avoided. Volume should ideally be between 200 and 300 ml [13,14]. The optimal framing rate is between 15 and 30 s, and not 60 s, which leads to significant reflux being missed [15]. The lungs should be clear of tracer activity normally, apart from a small contribution from early absorption of DTPA into the blood pool and extravascular tissues. Computer modelling and clinical data indicate that as little as 0.1 MBq of activity aspirated into the lung can be detected by the gamma camera [16]. There is some conflict in the reported reproducibility measures of visual interpretation techniques compared with analysis of time–activity curves. In one series, the computerized analysis was significantly better [17] whereas in another, visual interpretation appeared more accurate [18].

The two key findings of the current study are the unexpected proportion of patients who proceed to aspirate refluxate into the lungs in both groups. There is a clear and significant difference in the rates of lung aspiration between the GERD and the LPR patients. Although relatively small at 11/80 (14%) cases in the GERD group and high in the LPR group [48/205 (23%)], the finding is nevertheless significant as this is silent lung aspiration. This may partly explain associated, but apparently unrelated, conditions such a bronchiectasis [19] and lung fibrosis (Fig. 4) resulting from acid aspiration into the lungs [20,21]. Increasing tracer activity in the upper oesophagus was predictive of lung aspiration in patients with symptoms of LPR. There was a good correlation between the activity in the upper oesophagus, pharynx and lung aspiration in both patient groups.

Unlike pH monitoring, scintigraphy can detect nonacid reflux. Unlike multichannel impedance, it is less likely to suffer interference from normal respiratory activities. However, it measures reflux more coarsely, has a relatively short sampling time and cannot provide detailed information on the number or the nature of reflux episodes. It does not adequately convey an idea of the severity of the disease that informs the appropriateness of surgical intervention. This is critical as there are data showing that as few as three episodes of LPR per week may lead to significant laryngeal inflammation and injury [22]. Therefore, on the basis of data available in this study, scintigraphy seems to be primarily useful as a litmus test for pulmonary aspiration, which can stratify the link and lead to more invasive studies such as 24-h impedance and pH studies.

This raises two obvious questions: Does the presence of aspiration on scintigraphy correlate with other known objective measures of LPR, such as proximal exposure on 24 h pH and/or impedance monitoring? Does aspiration on scintigraphy indicate that surgery or medical treatment is likely to be successful? Work that has been submitted recently for publication by our group in 34 patients with chronic cough and LPR who underwent laparoscopic fundoplication provides a partial answer to these questions. As this was a highly selected group of patients with severe LPR, the finding of aspiration on scintigraphy in 50% of cases is probably not surprising. The symptomatic response rate to surgery was over 90%, suggesting that lung aspiration is very likely to be an indication for surgery. Furthermore, it is known that cough can also be triggered by nonacid or even basic refluxate because of previous sensitization of the airways or by reflex mediation [23]. There is also the potential for progressive lung disease in patients who continue to aspirate while on medical therapy alone.

This study also raises a number of questions that require more careful study and consideration. There is a significant age difference (7.7 years) between the patients with GERD versus the group with LPR. This suggests a much longer natural history of the disease in patients with LPR, which reflects the delay in diagnosis. Clinical awareness of the potential for silent LPR is a key factor just as it is in patients with ostensible GERD alone who may also have silent LPR. Scintigraphy offers a rapid and noninvasive method of screening such patients. These issues, however, require a careful prospective study.

Two drawbacks of the study are the retrospective collection of data and the different reporting standards for reflux scintigraphy that have evolved throughout the lifetime of the technique. The patients underwent scintigraphy over a period of 8 years, and in that time, our group has developed new methods of semiquantification and reporting. A study in which patients were recruited prospectively and that made use of a more detailed standard reporting template would provide greater data integrity for analysis. This is currently under way at a number of centres, which will further test the integrity and reproducibility of the technique. The main strengths of the study are the standardized approach to scintigraphy during the current study and the consistent clinical approach. All scintigraphic studies were carried out through a single service following a single protocol. Patients' histories were assessed by a single senior clinician or their locum, and categorized as GERD or LPR according to a consistent, standardized format. These assertions are supported by a power of 0.7 for the study, with a low likelihood of type I or II errors.

Conclusion

A high level of pulmonary aspiration was identified in this carefully selected patient group with LPR symptoms. The clinical history failed to identify significant reflux or aspiration in a high proportion of patients. There appears to be a significant difference in the height of reflux identified in GERD versus LPR patients. LPR symptoms and scintigraphy are associated significantly with pharyngeal isotope exposure. This study provides evidence for scintigraphic reflux studies in playing a role as a screening test for suspected LPR or lung aspiration associated with GERD.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Dickman R, Kim JL, Camargo L, Green SB, Sampliner RE, Garewal HS, Fass R. Correlation of gastroesophageal reflux disease symptoms characteristics with long-segment Barrett's esophagus. *Dis Esophagus* 2006; **19**:360–365.
2 Fass R, Dickman R. Clinical consequences of silent gastroesophageal reflux disease. *Curr Gastroenterol Rep* 2006; **8**:195–201.
3 Barry DW, Vaezi MF. Laryngopharyngeal reflux: more questions than answers. *Cleve Clin J Med* 2010; **77**:327–334.
4 Poelmans J, Tack J. Extraoesophageal manifestations of gastro-oesophageal reflux. *Gut* 2005; **54**:1492–1499.
5 Spechler SJ. Laryngopharyngeal reflux: a cause of faulty phonation or a faulted, phony diagnosis? *Clin Gastroenterol Hepatol* 2006; **4**:431–432.
6 Vaezi MF. Laryngitis and gastroesophageal reflux disease: increasing prevalence or poor diagnostic tests? *Am J Gastroenterol* 2004; **99**:786–788.
7 Hicks DM, Ours TM, Abelson TI, Vaezi MF, Richter JE. The prevalence of hypopharynx findings associated with gastroesophageal reflux in normal volunteers. *J Voice* 2002; **16**:564–579.
8 Dobhan R, Castell DO. Normal and abnormal proximal esophageal acid exposure: results of ambulatory dual-probe pH monitoring. *Am J Gastroenterol* 1993; **88**:25–29.
9 Charbel S, Khandwala F, Vaezi MF. The role of esophageal pH monitoring in symptomatic patients on PPI therapy. *Am J Gastroenterol* 2005; **100**:283–289.
10 Kahrilas PJ, Sifrim D. High-resolution manometry and impedance-pH/manometry: valuable tools in clinical and investigational esophagology. *Gastroenterology* 2008; **135**:756–769.
11 Zerbib F, Roman S, Bruley Des Varannes S, Gourcerol G, Coffin B, Ropert A, *et al*. Groupe Franais De Neuro-Gastroentérologie. Normal values of pharyngeal and esophageal 24-hour pH impedance in individuals on and off therapy and interobserver reproducibility. *Clin Gastroenterol Hepatol* 2013; **11**:366–372.
12 Ang D, Ang TL, Teo EK, Hsu PP, Tee A, Poh CH, *et al*. Is impedance pH monitoring superior to the conventional 24-h pH meter in the evaluation of patients with laryngorespiratory symptoms suspected to be due to gastroesophageal reflux disease? *J Dig Dis* 2011; **12**:341–348.
13 Russell C. Functional evaluation of the esophagus. In: Hill L, editor. *The esophagus medical and surgical management*. Philadelphia: WB Saunders; 1988. p. 45.
14 Shay SS, Abreu SH, Tsuchida A. Scintigraphy in gastroesophageal reflux disease: a comparison to endoscopy, LESp, and 24-h pH score, as well as to simultaneous pH monitoring. *Am J Gastroenterol* 1992; **87**:1094–1101.
15 Seymour JC, West JH, Drane WE. Sequential ten-second acquisitions for detection of gastroesophageal reflux. *J Nucl Med* 1993; **34**:658–660.
16 Ruth M, Carlsson S, Månsson I, Bengtsson U, Sandberg N. Scintigraphic detection of gastro-pulmonary aspiration in patients with respiratory disorders. *Clin Physiol* 1993; **13**:19–33.
17 Caglar M, Volkan B, Alpar R. Reliability of radionuclide gastroesophageal reflux studies using visual and time–activity curve analysis: inter-observer and intra-observer variation and description of minimum detectable reflux. *Nucl Med Commun* 2003; **24**:421–428.
18 Tuncel M, Kiratli PO, Aksoy T, Bozkurt MF. Gastroesophageal reflux scintigraphy: interpretation methods and inter-reader agreement. *World J Pediatr* 2011; **7**:245–249.
19 Piccione JC, McPhail GL, Fenchel MC, Brody AS, Boesch RP. Bronchiectasis in chronic pulmonary aspiration: risk factors and clinical implications. *Pediatr Pulmonol* 2012; **47**:447–452.
20 Lee JS, Collard HR, Raghu G, Sweet MP, Hays SR, Campos GM, *et al*. Does chronic microaspiration cause idiopathic pulmonary fibrosis? *Am J Med* 2010; **123**:304–311.
21 Raghu G. The role of gastroesophageal reflux in idiopathic pulmonary fibrosis. *Am J Med* 2003; **Suppl 3A** (Suppl 3A):60S–64S.
22 Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope* 1991; **101** (Pt 2 Suppl 53):1–78.
23 Patterson RN, Johnston BT, Ardill JE, Heaney LG, McGarvey LP. Increased tachykinin levels in induced sputum from asthmatic and cough patients with acid reflux. *Thorax* 2007; **62**:491–495.

World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v21.i12.3619

World J Gastroenterol 2015 March 28; 21(12): 3619-3627
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Clinical Trials Study

Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: A definitive diagnostic test?

Gregory L Falk, John Beattie, Alvin Ing, SE Falk, Michael Magee, Leticia Burton, Hans Van der Wall

Gregory L Falk, Sydney Heartburn Clinic, Gastroenterology, Concord Hospital, Sydney, NSW 2138, Australia
Gregory L Falk, University of Sydney, Sydney, NSW 2006, Australia
Gregory L Falk, Macquarie University, Sydney, NSW 2109, Australia
John Beattie, Ryde Medical Centre, Sydney, NSW 2112, Australia
Alvin Ing, Department of Respiratory Medicine, Concord Hospital, Sydney, NSW 2138, Australia
Alvin Ing, the University of Sydney, Sydney, NSW 2006, Australia
SE Falk, Sydney Heartburn Clinic, Gastroenterology, Sydney, NSW 2070, Australia
Michael Magee, Leticia Burton, Hans Van der Wall, Concord Nuclear Imaging Clinic, Sydney, NSW 2138, Australia
Author contributions: Falk GL originated the study, conducted the pH and manometry studies and contributed to the manuscript; Beattie J and Ing A contributed patients to the study, formulated the hypothesis and were involved in manuscript preparation; Falk SE collated the data and entered it into the spreadsheet and interviewed patients; Magee M, Burton L and Van der Wall H designed the scintigraphic study, interpreted the data and helped with statistical analysis and manuscript preparation.

Correspondence to: Hans Van der Wall, MBBS, PhD, FRACP, Concord Nuclear Imaging Clinic, 4 Hospital Road, Concord West, Sydney, NSW 2138, Australia. hvanderwall@gmail.com
Telephone: +61-2-97361040
Fax: +61-2-97362095
Received: May 2, 2014
Peer-review started: May 2, 2014
First decision: May 29, 2014
Revised: July 28, 2014
Accepted: October 15, 2014
Article in press: October 15, 2014
Published online: March 28, 2015

Abstract

AIM: To investigate the utility of scintigraphic studies in predicting response to laparoscopic fundoplication (LF) for chronic laryngopharyngeal reflux symptoms.

METHODS: Patients with upper aero-digestive symptoms that remained undiagnosed after a period of 2 mo were studied with conventional pH and manometric studies. Patients mainly complained of cough, sore throat, dysphonia and globus. These patients were imaged after ingestion of 99m-technetium diethylene triamine pentaacetic acid. Studies were quantified with time activity curves over the pharynx, upper and lower oesophagus and background. Late studies of the lungs were obtained for aspiration. Patients underwent LF with post-operative review at 3 mo after surgery.

RESULTS: Thirty four patients (20 F, 14 M) with an average age of 57 years and average duration of symptoms of 4.8 years were studied. Twenty four hour pH and manometry studies were abnormal in all patients. On scintigraphy, 27/34 patients demonstrated pharyngeal contamination and a rising or flat pharyngeal curve. Lung aspiration was evident in 50% of patients. There was evidence of pulmonary aspiration in 17 of 34 patients in the delayed study (50%). Pharyngeal contamination was found in 27 patients. All patients with aspiration showed pharyngeal contamination. In the 17 patients with aspiration, graphical time activity curve showed rising activity in the pharynx in 9 patients and a flat curve in 8 patients. In those 17 patients without pulmonary aspiration, 29% (5 patients) had either a rising or flat pharyngeal graph. A rising or flat curve predicted aspiration with a positive predictive value of 77% and a negative predictive value

of 100%. Over 90% of patients reported a satisfactory symptomatic response to LF with an acceptable side-effect profile.

CONCLUSION: Scintigraphic reflux studies offer a good screening tool for pharyngeal contamination and aspiration in patients with gastroesophageal reflux disease.

Key words: Laryngopharyngeal reflux; pH studies; Oesophageal manometry; Gastroesophageal reflux disease; Lung aspiration; Scintigraphy; Cough

Core tip: Scintigraphic studies offer a good screening tool for patients with gastroesophageal reflux disease (GERD) who are suspected of laryngopharyngeal reflux (LPR) and lung aspiration. Such studies can predict the response to fundoplication. Although the application for this study was in a highly selected group who underwent fundoplication for LPR, the results have been equally valid in over 700 unselected patients with suspected GERD. The technique however requires careful attention to detail for acquisition parameters, particularly with the volume of liquid into which the tracer is introduced.

Falk GL, Beattie J, Ing A, Falk SE, Magee M, Burton L, Van der Wall H. Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: A definitive diagnostic test? *World J Gastroenterol* 2015; 21(12): 3619-3627 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i12/3619.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i12.3619

INTRODUCTION

Gastro-oesophageal reflux disease (GERD) has a number of protean manifestations that make it difficult to diagnose and treat. In 2006, the Montreal Consensus Group defined GERD as "a condition which develops when the reflux of stomach contents causes troublesome symptoms or complications". The range of symptoms includes cough, sore throat and atypical chest pain and other apparent non-oesophageal symptoms. A proportion of patients may be asymptomatic even with significant acid reflux[1,2]. Furthermore, asymptomatic physiological episodes of GERD are a daily manifestation, further complicating the diagnosis[3].

While traditionally understood GERD (heartburn and regurgitation) is common, it has a different symptom profile to laryngopharyngeal reflux (LPR). The connection between GERD and LPR is however a contentious issue which has been canvassed in both the editorial format[4] and refereed publication[5]. These publications, especially the editorial by Spechler[4] rightly point out that not all chronic cough is due to GERD, as approximately half the patients treated for LPR do not have evidence of acid-reflux on pH monitoring[5]. We examined the connection between GERD and LPR in a small, selected population of patients referred for laparoscopic fundoplication as treatment for chronic cough and suspected pulmonary aspiration of refluxate. These patients had been carefully investigated and had established GERD by the standard criteria of pH and manometric studies. Detecting LPR and pulmonary aspiration are the two major blind spots of the accepted approach using pH and manometry, with some evidence that impedance studies may help with detecting LPR[6,7]. We examined the utility of scintigraphic reflux studies in the diagnosis of standard GERD, LPR and in the direct visualization of pulmonary aspiration of tracer during these studies.

MATERIALS AND METHODS

Population and clinical data

Patients were extracted from a research database for either proven or suspected GERD which had been approved by the Institutional Ethics Committee (LNR/12 CRGH/248). Consecutive patients undergoing laparoscopic fundoplication for suspected LPR disease on the basis of abnormal pH/manometry studies was extracted from this database. All patients were considered if they had predominantly upper respiratory tract symptoms that remained undiagnosed after 8 wk of investigation by appropriate specialists. Major upper respiratory tract symptoms documented were cough, sore throat, recurrent throat clearing, voice change, laryngospasm, aspiration, globus and regurgitation. Any history of heartburn regurgitation and dysphagia was also elicited. Because of the severity of continuing extra-oesophageal symptoms despite full medical management and results of standard investigations for GERD as the likely cause of LPR, patients were surgically treated by fundoplication. This is therefore a highly selected group of patients with a high pre-test probability of GERD causing LPR and with a long history of undiagnosed upper respiratory tract symptoms. Patients were reassessed clinically at three months following surgery for the severity of symptoms and/ or the degree of improvement in symptoms. Clinical data was prospectively collected using a standardized proforma before and after surgery and entered into a database.

Scintigraphy, pH studies and manometry were repeated in 5 patients with recurrent symptoms post-operatively.

pH monitoring (2 channel)

Ambulatory 24 h pH monitoring was performed using antimony crystal dual channel catheters (Medtronics, Synectics Medical, Minneapolis, Minnesota, United States) as described elsewhere. Data was recorded

Table 1 Patient symptom profile

Symptoms	Total (n = 34)
GERD	33
Heartburn	24
Regurgitation	23
LPR	33
Chronic cough	25
Voice change	15
Throat clearing/aspiration	11
Sore throat	10
Globus	5
Laryngospasm	2

GERD: Gastroesophageal reflux disease; LPR: Laryngopharyngeal reflux.

with a Digi trapper Mark Ⅲ recorder (Medtronics, Synectics Medical) and analysed with the Synectics PW esophagram reflux analysis module (Medtronics, Synectics Medical). Abnormal proximal reflux was based on results of previous studies[8].

Manometry

Stationary manometry was performed using a water perfused dent sleeve 8 channel catheter (Dent Sleeve International, Mississauga, Ontario, Canada) using standard techniques as described elsewhere. Data was recorded using a multichannel recording system (PC polygraph HR Medtronics, Synectics Medical, Minneapolis, Minnesota, United States) and analysed using PolyGram software program (Medtronics, Synectics Medical, Minneapolis, Minnesota, United States). Oesophageal motility was graded as normal, mildly, moderately or severely ineffective oesophageal motility modified from Kahrilas *et al*[9,10].

Scintigraphy

Patients were fasted overnight and medications were ceased for the 24 h prior to the test. While upright, patients were positioned in front of a Hawkeye 4 gamma camera (General Electric, Milwaukee, United States) with markers placed on the mandible and over the stomach to ensure the regions of interest were within the field of view of the camera. Patients swallowed 100-150 mL of water with 40-60 MBq of 99mTc DTPA followed by another 50 mL of water to clear the mouth and oesophagus of radioactivity. Dynamic images of the pharynx, oesophagus and stomach were obtained for 5 min at 15 s per frame into a 64 × 64 matrix. A second 30 min dynamic image was obtained in the supine position immediately following the upright study utilising 30 s frames. Following acquisition of the supine study, the patients were given a further 50 mL of water with 60 MBq of 99mTc phytate(colloid) followed by 50 mL of water as a flush. Delayed images were obtained at 2 h to assess the presence of aspiration of tracer activity into the lungs. Images were analysed by time activity curves over the pharynx, upper and lower half of the oesophagus and a background region over the right side of the chest, away from the stomach and oesophagus. Delayed images were analysed by a line profile over the lungs. Time activity curves were graded as showing no GERD, a falling curve, flat or rising curves. We defined the area under the curves (AUC) for the upper oesophagus and oropharynx after subtraction of the background level of activity as the Falk index.

Statistical analysis

Data was analysed by nonparametric statistical methods as much of the analysis was of ordinal data with multiple studies for each patient. Standard ANOVA statistics, Wilcoxon matched pairs test and Pearson correlation coefficient (2 tails) with significance levels of 0.05 were utilised. Cluster analysis of the principal variables was also undertaken to evaluate linkages between 11 key variables. The Statistica V8 software (Statsoft, Oklahoma, United States) package was used for data analysis.

RESULTS

Population and pre-operative clinical data

There were 34 patients (20 F, 14 M) with an average age of 57 years (range: 38-72 years). Proximal LPR symptoms were reported in 33 of 34 patients with one patient having no proximal symptoms, but severe heartburn and sinusitis. GERD was reported in 22 patients. Details of symptoms are provided in Table 1. Average duration of symptoms was 4.8 years (range: 0.5-22 years). All patients underwent laparoscopic fundoplication on the basis of symptoms, supporting tests and failure of best medical management (including double-dose proton pump inhibitor therapy).

Post-operative clinical data

Patients remained on anti-reflux medical therapy for six weeks post-operatively with cessation prior to the 3 mo review. At three months, total control of symptoms was reported in 27 (79%), partial in 4, giving overall improvement in 31 (91%). The rate of dysphagia was unchanged in 12 (44%). Occasional chest pain and bloating was present in 4, reduction in cough frequency in 1 and continued heartburn but eliminated cough in 1. Scintigraphy demonstrated low-grade reflux to the mid-oesophagus but not the pharynx in this patient. Reappearance of cough on stopping PPI occurred in 2 and no symptom resolution in 1 despite normalisation of scintigraphy and 24-h pH monitoring. Two patients were lost to review. Scintigraphy showed recurrent reflux to the pharynx in the 2 former patients and no evidence of reflux in the latter. The pH study was also normal in the latter patient.

Statistical analysis

Cough was the only significant symptom predicting

Table 2 pH studies

pH studies	mean ± SD	Range	
		Minimum	Maximum
pH distal episodes	128.06 ± 91.41	8	356
pH distal %total time	16.04 ± 19.22	5.2	105
pH distal erect exposure	15.68 ± 18.72	4.2	102
pH distal sup exposure	20.10 ± 29.35	13	102
pH proximal episodes	31.30 ± 38.48	11	145
pH proximal %total time	1.59 ± 2.11	1	9.7
pH prox erect exposure	4.68 ± 17.65	0	102
pH prox sup exposure	10.52 ± 29.49	2	102

pharyngeal contamination by scintigraphy (P = 0.047) and voice change predicted aspiration by scintigraphy (P = 0.038). All symptoms were strongly correlated with pharyngeal contamination by scintigraphy. Cough, laryngospasm and globus were strongly correlated with aspiration (scintigraphy). Change in voice was present in 15 patients, 11 demonstrated aspiration and 13 pharyngeal contamination by scintigraphy.

24 h two channel pH studies

The 24 h pH studies were abnormal in all patients (Table 2). Episodes of reflux/24 h in the distal oesophagus were a mean of 128 and in the upper oesophagus, a mean of 31. The acid reflux exposure time distal was a mean of 16%, and 20% when supine. Reflux exposure time proximal was a mean 1.6%/24 h and 10.5% when supine. There were strong correlations between all symptoms and each of the proximal 24-h pH parameters. Strong correlations were found for heartburn, regurgitation and distal pH results. Strong correlations were found between severity of pH results and pulmonary aspiration by scintigraphy.

Manometry

Lower oesophageal sphincter pressure had a mean ± SD of 2.94 ± 5.03 (normal > 18, range: 0-18 mmHg). Oesophageal motility was frequently abnormal and graded as severe IEM in 16, moderate IEM in 4, mild IEM in 5 and normal in 9. Highly significant correlations were found between impaired motility and pulmonary aspiration (P = 0.000063), episodes of reflux by scintigraphy (P = 0.000011), amplitude of reflux by scintigraphy (P = 0.0026) and the Falk index (AUC) (P = 0.000001).

Scintigraphic studies

There was evidence of pulmonary aspiration in 17 of 34 patients in the delayed study (50%). Pharyngeal contamination was found in 27 patients. All patients with aspiration showed pharyngeal contamination. In the 17 patients with aspiration, graphical time activity curve showed rising activity in the pharynx in 9 patients and a flat curve in 8 patients. In those 17 patients without pulmonary aspiration, 29% (5 patients) had either a rising or flat pharyngeal graph. A rising or flat curve predicted aspiration with a positive predictive value of 77% and a negative predictive value of 100%. There was a significant correlation between pharyngeal contamination and aspiration (P = 0.000). All patients in the cohort had evidence of gastro-oesophageal reflux by scintigraphy. Significant correlations were found for almost all pH studies and the isotope episodes, and amplitude of reflux in the oesophagus by scintigraphy (P < 0.01) but not for proximal supine acid exposure.

Cluster analysis

The hierarchical tree relationship between variables was expressed as a vertical icicle plot of the 11 variables (Figure 1) with single linkages using non-standardised Euclidean distances[11]. Tight linkages were shown between positive pharyngeal scintigraphy, aspiration by scintigraphy, manometric motility studies and impaired oesophageal motility, proximal total and exposure time.

DISCUSSION

When assessing patients for persistent upper respiratory tract symptoms (predominantly cough) and no cause is immediately apparent, there is accumulated clinical evidence to consider the possibility of LPR. However, approximately 30% of the population in one series of 2000 random cases had a score of over 10 in the reflux symptom index[12] with 75% also complaining of symptomatic GERD[13] (Figure 2). The task of assessing GERD in such a vast number of patients is problematic as there would be the need for a relatively invasive algorithm of endoscopy, pH/manometry/ impedance monitoring, ENT examination, respiratory function studies, amongst others. This would incur substantial costs and patient inconvenience. Endoscopy shows abnormalities in less than 50% of patients with reflux disease[14]. The presence of pepsin in saliva has shown promise as a surrogate marker of GERD that reaches the pharynx[15,16] but does not indicate lung aspiration of refluxate. A simple non-invasive test is required to assess the presence of significant full-column or proximal oesophageal reflux with potential for pharyngeal contamination and pulmonary aspiration of gastric contents. This particular standardised protocol for scintigraphy has the potential to be such an option.

Two channel 24 h pH monitoring provides a good measure of the frequency, severity and percentage of various aspects of acidic reflux. It may demonstrate full-column reflux rising to the level of the cricopharyngeus, and so a likelihood of pharyngeal contamination (Figure 3). However recent work using impedance studies has demonstrated that many patients suffer reflux which is not identified on pH monitoring but remains symptomatic and potentially damaging[17,18]. The pH study does not measure the presence of acid or non-

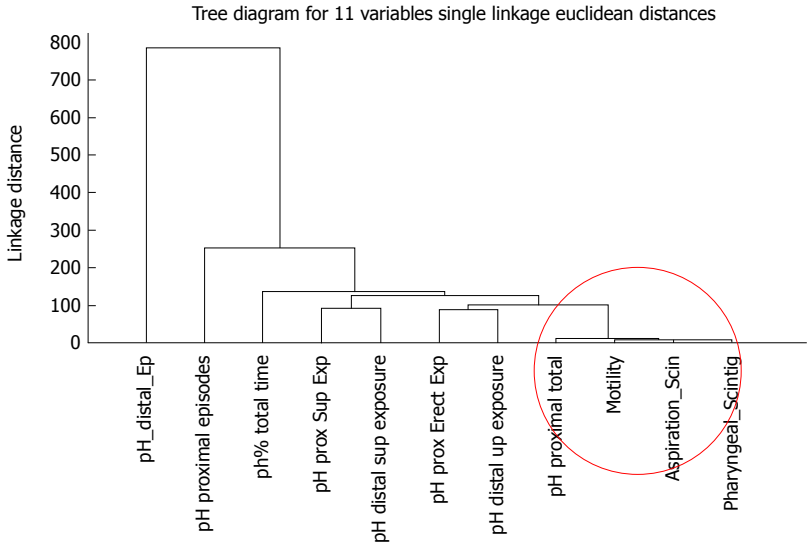


Figure 1 Cluster analysis of variables. There is tight clustering of pH proximal total exposure, Motility, Aspiration scintigraphy and Pharyngeal scintigraphy located at the far right side of the graph.

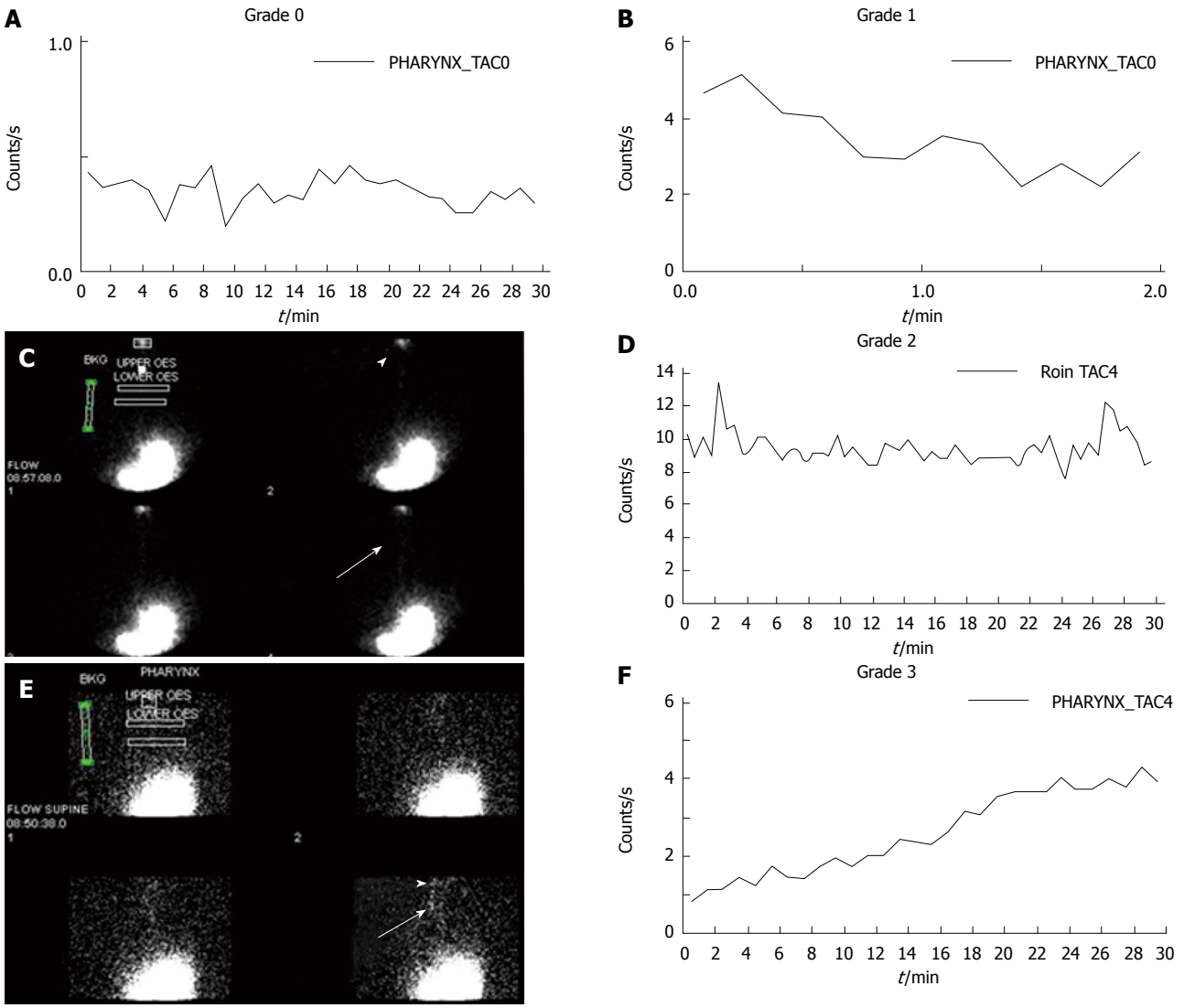


Figure 2 Grading of time-activity curves for the pharynx and upper oesophagus. A: Grade 0 is where there is no significant activity and the curve is similar to the background time-activity curve; B: Grade 1 reflects activity that clears with a falling curve; C, D: Grade 2 is a time activity curve that correlates with activity in the pharynx (arrowhead) and oesophagus (arrow) that fails to clear; E, F: Grade 3 is a rising time-activity curve that indicates progressive gastro-oesophageal reflux (arrowhead and arrow) that indicates rising activity in the pharynx and upper oesophagus respectively.

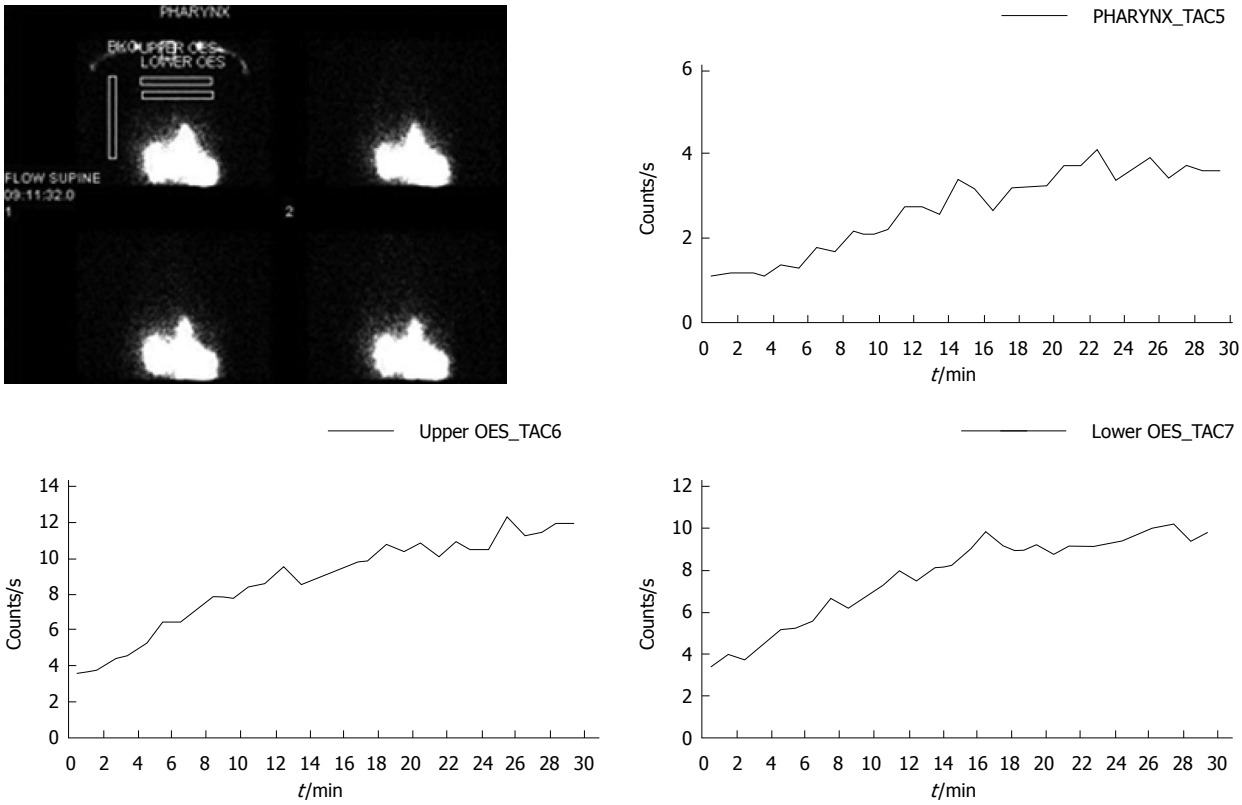


Figure 3 Full column reflux with rising time-activity curves over the pharynx, upper and lower oesophagus. The diagram shows the typical regions of interest from which the data is derived.

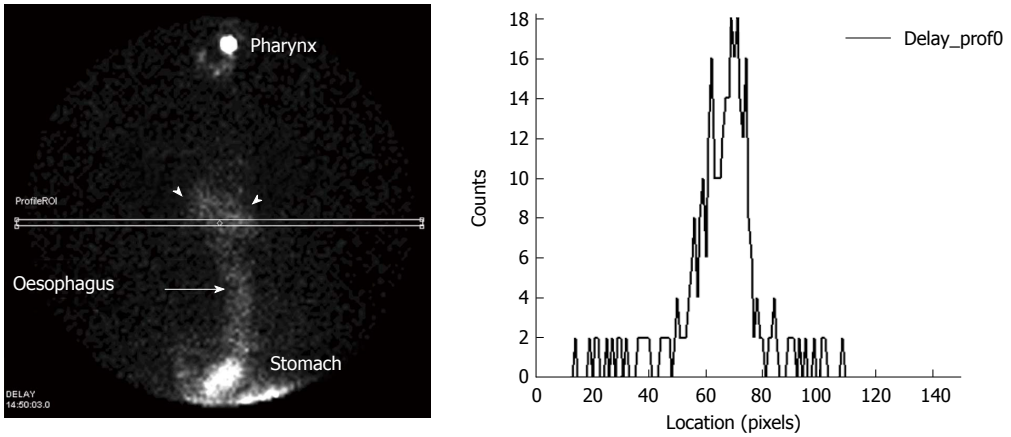


Figure 4 Typical image of the delayed study in which tracer activity is present in the main airways in a patient with lung aspiration.

acid material in the pharynx[19]. One clear advantage of reflux scintigraphy is that it measures any reflux to the level of the pharynx and the direct occurrence of pulmonary aspiration. It is not dependent upon measuring acid. A rising time-activity curve over the pharynx was demonstrably a good predictor of pulmonary aspiration in this group of patients. It very likely indicates continuing episodes of GERD combined with a failure of normal clearance mechanisms due to impaired motility. A flat pharyngeal time-activity curve may indicate a failure of pharyngeal clearance in the absence of repeated episodes of GERD into the pharynx. This relationship is reflected in the correlation between the manometric motility studies which measure ineffective oesophageal clearance of acid[10] and the presence of pulmonary aspiration on scintigraphy.

Upper aero-digestive symptoms and positive pharyngeal scintigraphy were strongly associated when analysed as paired variables on an individual patient basis. Cough, laryngospasm and globus were strongly correlated with positive aspiration scintigraphy. This suggests an aetiological role for the persistence of reflux (acid or weakly acidic/alkaline) fluid in the pharynx and subsequent aspiration into the respiratory

tract (Figure 4). There is evidence that this may directly trigger the cough reflex[20] or lower the threshold for the cough reflex as indicated by C2 and C5 testing[21]. The concept of direct damage is supported by the findings in the 25 cases of chronic cough, where 14 cases had aspiration and 23 pharyngeal contamination by scintigraphy. The alternate theory of chronic cough mediated by afferent nerves in the distal oesophagus is also well supported in other studies[22]. There is no reason to suppose that both mechanisms are not separately operative in individual patients or indeed concurrent as there was no way to identify reflex-mediated patients. However, scintigraphic findings in the current study are not congruent with the concept of a reflex-mediated aetiology as the majority of the patients with cough, laryngospasm and globus had evidence of direct contamination of the pharynx and lungs. Perhaps reflex mediation may be more frequent in a less pathological group. The scintigraphic studies have shown a surprising degree of pulmonary aspiration (50%) in patients with cough. This may reflect the very highly and conservatively selected group of patients with long disease duration, likely to have more severe disease than in other reported series.

The ultimate test of the predictive value of reflux scintigraphic findings has been the symptomatic response to definitive surgical management by laparoscopic fundoplication. Resolution of laryngopharyngeal symptoms were found in 90% of cases. This supports the choice of patients for intervention based on the scintigraphic findings. It is no surprise that there has been a continuation of dysphagia in this patient group with a large percentage of oesophageal dysmotility. It is of course possible that there may have been a strong placebo effect within this patient group, which has been reported to be as high as 85% in chronic cough treated with pharmacological intervention such as opiates. However, opiates also have centralised effects upon cerebral neurotransmitters[23]. Surgical intervention in this situation is however more likely to have a response rate closer to 35%, which is generally accepted for the placebo effect[24]. The one patient that had no response to surgery had no definable reflux by pH monitoring or scintigraphy on follow-up. It does demonstrate the complexity of the disease where there may be a mixed pathology of both GERD and primary respiratory disease or a behavioral component. In a large multicentre study of laparoscopic fundoplication for GERD with 5 year follow-up in 1340 patients, symptoms were satisfactorily treated in 93% of patients[25]. More applicable to this study is a group of 47 patients reported over a six year period having laparoscopic fundoplication for the treatment of chronic cough[26]. Symptom relief was reported in 30 (64%) with a similar side-effect profile. The use of reflux scintigraphy may have yielded substantially better primary symptom management by improved selection as in our series.

Scintigraphic studies have been utilized to evaluate pulmonary aspiration in infants and children for many years, generally as tracer being instilled in milk which is administered at night with scanning the following morning[27,28]. These studies have been performed with low radiation exposure, often as low as single chest x-ray examinations and are considered safe and acceptable. Modifications of the technique have been shown to provide good results in the detection of GERD[29-32] and lung aspiration of refluxate[33,34]. Results in these series tend to vary with technical differences[29,31,35,36]. It appears that the volume of liquid in which the tracer is introduced into the stomach is important, as is the framing rate for study acquisition. The optimal volume is reported between 150 and 300 mL[29,31,32] and framing rates between 15 and 30 s, not 60 s which leads to significant reflux being missed[37]. Computer modeling and clinical data indicates that as little as 0.1 MBq of activity aspirated into the lung can be detected by the gamma camera[34]. There is some conflict in the reported reproducibility measures of visual interpretation *vs* analysis of time-activity curves. In one series, the computerised analysis was significantly better[38] while in another, visual interpretation was better[39]. These differences very likely reflect variations in the acquisition parameters. Importantly, reproducibility was good in both studies with kappa values greater than 0.70. Acquisition protocols in the current study were aligned with the technique of Caglar *et al*[38]. Two groups have reported good sensitivity and utility of the scintigraphic technique for the detection of laryngeal reflux and aspiration of tracer into the lungs[35,36]. The study of Bestetti *et al*[35] reported 201 patients with symptomatic posterior laryngitis documented by laryngoscopy and who were evaluated after administration of 300 mL of orange juice labeled with 99mTc. GERD was demonstrated by scintigraphy in 134 (67%), of which 78% was proximal and 31 patients were positive on scintigraphy for pulmonary aspiration. These findings are similar to the current report. Symptoms profiles were also similar between the study of Bestetti *et al*[35] and our group. Proximal symptoms in our group were tightly correlated with positive pharyngeal contamination. Cough was the only significant variable predicting positive pharyngeal contamination by multivariate analysis. Voice change was the only variable that predicted positive pulmonary aspiration by multivariate analysis. This finding has clinical importance. Our study showed good concordance for oesophageal scintigraphy with the 24 h pH and motility findings on an individual patient basis as paired studies. Other have reported less favourable results for scintigraphy (82% for pH studies *vs* 33% for scintigraphy)[31]. This may reflect a different and less severe patient sample. Technical difference may also have contributed to these disparate findings.

This study is relatively small and collected over a

four year period. Such studies are time-consuming and invasive and patient compliance becomes a significant issue. The use of patient questionnaires raises the problem of the degree of placebo effect[40]. There were a large number of uncontrolled variables in the study and a high degree of patient variability, especially in the pH studies. A valid approach is therefore to consider these variable as dependant paired studies on an individual basis, as none of the variables were held constant. Cluster analysis was a valuable tool to assess a large number of variables and identify fundamental linkages between variables to get a sense of connectedness[11]. The finding of strong linkages between the motility studies, pH proximal total exposure time, pharyngeal and aspiration scintigraphy is reassuring.

The findings of the current study indicate that reflux scintigraphy utilising the current protocol is a potential screening tool for pharyngeal contamination and lung aspiration if GERD is suspected in patients with cough or other LPR symptoms. This requires further study in a more mixed and less selected group of patients. Subsequent assessment in over 700 patients has shown further utility in predicting response to surgical intervention and more importantly, factors that may predict surgical failure. The technique is simple, reproducible and has a low radiation exposure that is considered acceptable even in a pediatric population. The patient group with long-term LPR symptoms, especially cough and extensive investigation over a long time course can be selected for a high likelihood of symptomatic improvement by laparoscopic fundoplication. The combination of reflux scintigraphy, motility studies and two channel 24 h pH monitoring can increase the likelihood of success to over 90%. Patients with cough should therefore be assessed for pulmonary aspiration.

COMMENTS

Background

Gastroesophageal reflux disease (GERD) is a common occurrence which may however be asymptomatic and extend to laryngopharyngeal reflux (LPR) and lung aspiration of refluxate. Patients may not have symptoms of GERD but present with typical upper respiratory tract symptoms such as cough, dysphonia and globus. A high clinical index of suspicion is necessary to make the connection. Scintigraphy has the potential to screen for both LPR and lung aspiration.

Research frontiers

Assessing LPR, lung aspiration and predicting the response to surgical therapy with laparoscopic fundoplication is the key to successful therapy. The necessary extension to this is discovering factors that predict failure of surgical therapy. Scintigraphic reflux studies have the potential to perform both tasks.

Innovations and breakthroughs

Impedance studies may prove to be reliable in the assessment of LPR as would salivary pepsin assays. The additive value to pH studies and high resolution manometry may prove to be decisive in the therapy of LPR.

Applications

Scintigraphy may prove to be a good predictor of successful laparoscopic fundoplication in terms of the presence of both LPR and lung aspiration of refluxate. More importantly it may be able to predict failure of surgery, especially in patients with co-existent gastroparesis. Post-operative assessment may provide important information regarding effectiveness of the fundoplication.

Terminology

Scintigraphy uses the common isotope 99m Technetium which has a half-life of 6 h and a low radiation exposure at the doses being used. It is commonly bound to diethylene triamine pentaacetic acid which is frequently used in renal studies.

Peer-review

The true possible diagnostic role of scintigraphy in LPR might not be so straightforward as hypothesized, and will need more evaluations. Functional components to the symptoms may not be negligible in patients classified as having LPR, thus making more difficult a correct diagnosis, even in case of a positive scintigraphy test.

REFERENCES

1 **Dickman R**, Kim JL, Camargo L, Green SB, Sampliner RE, Garewal HS, Fass R. Correlation of gastroesophageal reflux disease symptoms characteristics with long-segment Barrett's esophagus. *Dis Esophagus* 2006; **19**: 360-365 [PMID: 16984533 DOI: 10.1111/j.1442-2050.2006.00606.x]

2 **Fass R**, Dickman R. Clinical consequences of silent gastro-esophageal reflux disease. *Curr Gastroenterol Rep* 2006; **8**: 195-201 [PMID: 16764785]

3 **Richter JE**. Typical and atypical presentations of gastroesophageal reflux disease. The role of esophageal testing in diagnosis and management. *Gastroenterol Clin North Am* 1996; **25**: 75-102 [PMID: 8682579]

4 **Spechler SJ**. Laryngopharyngeal reflux: a cause of faulty phonation or a faulted, phony diagnosis? *Clin Gastroenterol Hepatol* 2006; **4**: 431-432 [PMID: 16616346 DOI: 10.1016/j.cgh.2006.01.012]

5 **Vaezi MF**. Laryngitis and gastroesophageal reflux disease: increasing prevalence or poor diagnostic tests? *Am J Gastroenterol* 2004; **99**: 786-788 [PMID: 15128337 DOI: 10.1111/j.1572-0241.2004.40290.x]

6 **Yuksel ES**, Vaezi MF. Therapeutic strategies for laryngeal manifestations of gastroesophageal reflux disease. *J Clin Gastroenterol* 2013; **47**: 195-204 [PMID: 23340061 DOI: 10.1097/MCG.0b013e31827458f9]

7 **Smith JA**, Abdulqawi R, Houghton LA. GERD-related cough: pathophysiology and diagnostic approach. *Curr Gastroenterol Rep* 2011; **13**: 247-256 [PMID: 21465223 DOI: 10.1007/s11894-011-0192-x]

8 **Dobhan R**, Castell DO. Normal and abnormal proximal esophageal acid exposure: results of ambulatory dual-probe pH monitoring. *Am J Gastroenterol* 1993; **88**: 25-29 [PMID: 8420269]

9 **Kahrilas PJ**, Dent J, Dodds WJ, Hogan WJ, Arndorfer RC. A method for continuous monitoring of upper esophageal sphincter pressure. *Dig Dis Sci* 1987; **32**: 121-128 [PMID: 3803142]

10 **Kahrilas PJ**, Dodds WJ, Hogan WJ, Kern M, Arndorfer RC, Reece A. Esophageal peristaltic dysfunction in peptic esophagitis. *Gastroenterology* 1986; **91**: 897-904 [PMID: 3743966]

11 **Ward JH, Jr**. Hierarchical Grouping to Optimize an Objective Function. *J Am Statistical Assoc* 1963; **58**: 236-244

12 **Koufman JA**, Aviv JE, Casiano RR, Shaw GY. Laryngopharyngeal reflux: position statement of the committee on speech, voice, and swallowing disorders of the American Academy of Otolaryngology-Head and Neck Surgery. *Otolaryngol Head Neck Surg* 2002; **127**: 32-35 [PMID: 12161727]

13 **Kamani T**, Penney S, Mitra I, Pothula V. The prevalence of laryngopharyngeal reflux in the English population. *Eur Arch Otorhinolaryngol* 2012; **269**: 2219-2225 [PMID: 22576243 DOI: 10.1007/s00405-012-2028-1]

14 **Cantù P**, Savojardo D, Carmagnola S, Penagini R. Impact of referral for gastro-oesophageal reflux disease on the workload of an academic Gastroenterology Unit. *Dig Liver Dis* 2005; **37**: 735-740 [PMID: 16024304 DOI: 10.1016/j.dld.2005.04.025]

15 **Vaezi MF**, Richter JE. Twenty-four-hour ambulatory esophageal pH monitoring in the diagnosis of acid reflux-related chronic cough. *South Med J* 1997; **90**: 305-311 [PMID: 9076302]

16 **Vakil N**. Salivary pepsin to diagnose GORD? *Gut* 2015; **64**: 361-362 [PMID: 25056658 DOI: 10.1136/gutjnl-2014-307485]
17 **Sifrim D**, Blondeau K, Mantillla L. Utility of non-endoscopic investigations in the practical management of oesophageal disorders. *Best Pract Res Clin Gastroenterol* 2009; **23**: 369-386 [PMID: 19505665 DOI: 10.1016/j.bpg.2009.03.005]
18 **Aanen MC**, Bredenoord AJ, Samsom M, Smout AJ. Reliability of oesophageal pH recording for the detection of gastro-oesophageal reflux. *Scand J Gastroenterol* 2008; **43**: 1442-1447 [PMID: 18756402 DOI: 10.1080/00365520802308003]
19 **Zerbib F**, Roman S, Bruley Des Varannes S, Gourcerol G, Coffin B, Ropert A, Lepicard P, Mion F. Normal values of pharyngeal and esophageal 24-hour pH impedance in individuals on and off therapy and interobserver reproducibility. *Clin Gastroenterol Hepatol* 2013; **11**: 366-372 [PMID: 23142603]
20 **Patterson RN**, Johnston BT, Ardill JE, Heaney LG, McGarvey LP. Increased tachykinin levels in induced sputum from asthmatic and cough patients with acid reflux. *Thorax* 2007; **62**: 491-495 [PMID: 17251314 DOI: 10.1136/thx.2006.063982]
21 **Qiu Z**, Yu L, Xu S, Liu B, Zhao T, Lü H, Qiu Z. Cough reflex sensitivity and airway inflammation in patients with chronic cough due to non-acid gastro-oesophageal reflux. *Respirology* 2011; **16**: 645-652 [PMID: 21342332 DOI: 10.1111/j.1440-1843.2011.01952.x]
22 **Irwin RS**. Chronic cough due to gastroesophageal reflux disease: ACCP evidence-based clinical practice guidelines. *Chest* 2006; **129**: 80S-94S [PMID: 16428697 DOI: 10.1378/chest.129.1_suppl.80S]
23 **Eccles R**. The powerful placebo in cough studies? *Pulm Pharmacol Ther* 2002; **15**: 303-308 [PMID: 12099783 DOI: 10.1006/pupt.2002.0364]
24 **Beecher HK**. The powerful placebo. *J Am Med Assoc* 1955; **159**: 1602-1606 [PMID: 13271123]
25 **Pessaux P**, Arnaud JP, Delattre JF, Meyer C, Baulieux J, Mosnier H. Laparoscopic antireflux surgery: five-year results and beyond in 1340 patients. *Arch Surg* 2005; **140**: 946-951 [PMID: 16230543]
26 **Faruqi S**, Sedman P, Jackson W, Molyneux I, Morice AH. Fundoplication in chronic intractable cough. *Cough* 2012; **8**: 3 [PMID: 22812601 DOI: 10.1186/1745-9974-8-3]
27 **Collier BD**. Detection of aspiration: scintigraphic techniques. *Am J Med* 1997; **103**: 135S-137S [PMID: 9422639]
28 **Maurer AH**, Parkman HP. Update on gastrointestinal scintigraphy. *Semin Nucl Med* 2006; **36**: 110-118 [PMID: 16517233 DOI: 10.1053/j.semnuclmed.2005.12.003]
29 **Kjellén G**, Brudin L, Håkansson HO. Is scintigraphy of value in the diagnosis of gastrooesophageal reflux disease? *Scand J Gastroenterol* 1991; **26**: 425-430 [PMID: 2034995]
30 **Russell C**. Functional evaluation of the esophagus. In: Hill L, editor. The Esophagus Medical and surgical management. Philadelphia: WB Saunders, 1988: 45
31 **Shay SS**, Abreu SH, Tsuchida A. Scintigraphy in gastroesophageal reflux disease: a comparison to endoscopy, LESp, and 24-h pH score, as well as to simultaneous pH monitoring. *Am J Gastroenterol* 1992; **87**: 1094-1101 [PMID: 1519565]
32 **Thomas EJ**, Kumar R, Dasan JB, Kabra SK, Bal CS, Menon S, Malhothra A. Gastroesophageal reflux in asthmatic children not responding to asthma medication: a scintigraphic study in 126 patients with correlation between scintigraphic and clinical findings of reflux. *Clin Imaging* 2003; **27**: 333-336 [PMID: 12932685]
33 **Ravelli AM**, Panarotto MB, Verdoni L, Consolati V, Bolognini S. Pulmonary aspiration shown by scintigraphy in gastroesophageal reflux-related respiratory disease. *Chest* 2006; **130**: 1520-1526 [PMID: 17099032 DOI: 10.1378/chest.130.5.1520]
34 **Ruth M**, Carlsson S, Månsson I, Bengtsson U, Sandberg N. Scintigraphic detection of gastro-pulmonary aspiration in patients with respiratory disorders. *Clin Physiol* 1993; **13**: 19-33 [PMID: 8382143]
35 **Bestetti A**, Carola F, Carnevali-Ricci P, Sambataro G, Tarolo GL. 99mTc-sulfur colloid gastroesophageal scintigraphy with late lung imaging to evaluate patients with posterior laryngitis. *J Nucl Med* 2000; **41**: 1597-1602 [PMID: 11037986]
36 **Galli J**, Volante M, Parrilla C, Rigante M, Valenza V. Oropharyngoesophageal scintigraphy in the diagnostic algorithm of laryngopharyngeal reflux disease: a useful exam? *Otolaryngol Head Neck Surg* 2005; **132**: 717-721 [PMID: 15886624 DOI: 10.1016/j.otohns.2005.01.043]
37 **Seymour JC**, West JH, Drane WE. Sequential ten-second acquisitions for detection of gastroesophageal reflux. *J Nucl Med* 1993; **34**: 658-660 [PMID: 8455084]
38 **Caglar M**, Volkan B, Alpar R. Reliability of radionuclide gastroesophageal reflux studies using visual and time-activity curve analysis: inter-observer and intra-observer variation and description of minimum detectable reflux. *Nucl Med Commun* 2003; **24**: 421-428 [PMID: 12673171 DOI: 10.1097/01.mnm.0000068297.89730.19]
39 **Tuncel M**, Kıratlı PO, Aksoy T, Bozkurt MF. Gastroesophageal reflux scintigraphy: interpretation methods and inter-reader agreement. *World J Pediatr* 2011; **7**: 245-249 [PMID: 21822991 DOI: 10.1007/s12519-011-0322-4]
40 **Hróbjartsson A**, Gøtzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. *J Intern Med* 2004; **256**: 91-100 [PMID: 15257721 DOI: 10.1111/j.1365-2796.2004.01355.x]

P- Reviewer: Contini S, Mittal SK **S- Editor**: Gou SX **L- Editor**: A **E- Editor**: Ma S

GIANT HIATUS HERNIA

The clinical situation of Giant hiatus hernia has proved to be one of the more difficult abnormalities to diagnose as symptoms are not typical of the usual hiatus hernia with heartburn and regurgitation, but are rather structural or entrapment, giving pain, abnormality swallowing, early satiety and dyspnoea. Patients were frequently considered by gastroenterology to be too unwell with respiratory symptoms to undergo repair because of dyspnoea and chest pain, of an otherwise troublesome and potentially lethal trapped hiatus hernia. The condition was poorly understood in general medical circles and symptoms poorly recognised.

It became apparent when operating on patients who were considerably compromised both with gastric symptoms and respiratory symptoms that the respiratory symptoms diminished greatly following surgery, which led to my pursuing a long-standing program to develop an understanding of the hiatal hernia abnormality which caused the respiratory symptoms.

It did not seem unreasonable that a large mass of stomach in the chest would impede respiratory function. Therefore, initially investigation of the effect of the mediastinal mass of the large hiatus hernia on pulmonary function was undertaken before and after surgery. There had been some work in the 1970s assessing pulmonary function in patients with hiatus hernia which did not really elucidate the issue until the first publication of a paired series of observations in a cohort of patients operated by myself, by my junior associate Jackie Zhu. The dyspnoea was found improved following surgical correction, but the pulmonary function did not improve significantly after surgery, on respiratory laboratory function testing. Alternative explanations were sought, concentrating more on the cardiac compromise secondary to the presence of the giant hiatus hernia in the mediastinum behind the heart.

This led to the ongoing investigation predominantly using stress echocardiography in a multitude of ways, and also CT and MRI scanning which demonstrated the effect upon cardiac output by the

presence of the large hernia in the mediastinum. At this stage it became apparent in paired studies that a major effect causing dyspnoea was cardiac in origin with minimal but significant change on pulmonary function also. This series of publications were well received worldwide and has largely changed what used to be a nihilistic practice of management, into a practice which repaired the hernia, improved the respiratory symptomatology and enhanced patient's well-being. Dyspnoea is now generally recognised as a consequence of giant hiatus hernia. Our initial papers were editorialised in the journal of the American College of cardiology and have been well cited, indicating a wide dissemination of this knowledge and subsequent influence on the practice of cardiology. The symptom of dyspnoea in the presence of giant hiatal herniation has become well recognised in the surgical literature as a symptom of the disease requiring alleviation.

Additionally, surgery of the giant hiatus hernia required repair of a very major anatomical abnormality of the diaphragm , and so the potential for longer term recurrence of the hernia was high. Multiple different technological advances were evaluated with a view to reducing the rate of surgical recurrence. Animal study was undertaken to evaluate efficacy of mesh. Multiple different techniques were evaluated. The next series of publications demonstrate a concerted effort to assess the various surgical techniques in the attempt to reduce recurrence rates and recurrent reflux symptomatology in one of the largest experiences of the condition in the world. It appears to be, to the best of my knowledge, the largest single surgeon experience in the world of giant hiatus hernia surgery, which has enabled a substantive evaluation of the potential technique. This work has had a major effect upon national and international management of this situation, with multiple international fully trained surgeons coming from the Americas, Europe and the UK to work in my unit and learn these techniques. The international influence was also in evidence by my invitation to speak as visiting Professor at the National upper gastrointestinal surgeons meeting in the UK in 2016. I am also frequently asked to speak at national meetings on the giant hiatus hernia.

References:

1. Lee F, Khoma O, Mendu M, Falk G. Does composite repair of giant paraoesophageal hernia improve patient outcomes? ANZ J Surg. 2021;91(3):310-5.

2. Khoma O, Mugino M, Falk GL. Is repairing giant hiatal hernia in patients over 80 worth the risk? Surgeon. 2020;18(4):197-201.

3. Falk GL, Archer L, Gooley SC. Is fundoplication advisable in repair of para-oesophageal hernia? “Little operation” or “big operation”? European Surgery. 2020;52(6):277-81.

4. Falk GL, D’Netto TJ, Little SC. Giant hiatus hernia: closure of the difficult hiatus. European Surgery. 2019;51(6):291-4.

5. Furtado RV, Vivian SJ, van der Wall H, Falk GL. Medium-term durability of giant hiatus hernia repair without mesh. Ann R Coll Surg Engl. 2016;98(7):450-5.

6. Furtado RV, D'Netto TJ, Hook HC, Falk GL, Vivian S. Massive hiatus hernia complicated by jaundice. J Surg Case Rep. 2015;2015(7):rjv087.

7. Le Page PA, Furtado R, Hayward M, Law S, Tan A, Vivian SJ, et al. Durability of giant hiatus hernia repair in 455 patients over 20 years. The Annals of The Royal College of Surgeons of England. 2015;97(3):188-93.

8. D'Netto TJ, Falk GL. A technique for the laparoscopic repair of paraoesophageal hernia without mesh. J Gastrointest Surg. 2014;18(4):851-7; discussion 7.

9. Furtado R, Le Page P, Falk G. ‘Pantaloon’ diaphragmatic hernia masquerading as a paraoesophageal hiatal hernia. ANZ Journal of Surgery. 2013;83(12):994-5.

10. Smith GS, Hazebroek EJ, Eckstein R, Berry H, Smith WM, Isaacson JR, et al. Evaluation of Dual Mesh for repair of large hiatus hernia in a porcine model. Surg Endosc. 2008;22(7):1625-31.

11. Kelty CJ, Falk GL. Mesh repairs in hiatal surgery. The case against mesh repairs in hiatal surgery. Ann R Coll Surg Engl. 2007;89(5):479-81.

UPPER GUT

Royal Australasian College of Surgeons

Does composite repair of giant paraoesophageal hernia improve patient outcomes?

Felix Lee ,* Oleksandr Khoma,*† Maite Mendu‡ and Gregory Falk*‡§

*Department of Upper Gastro-Intestinal Surgery, Concord Repatriation General Hospital, Sydney, New South Wales, Australia
†Department of Postgraduate Research, School of Medicine, The University of Notre Dame Australia, Perth, Western Australia, Australia
‡Department of Research, Sydney Heartburn Clinic, Sydney, New South Wales, Australia and
§School of Medicine, The University of Sydney, Sydney, New South Wales, Australia

Key words
giant hiatus hernia, laparoscopic fundoplication, paraoesophageal hiatus hernia, quality of life, recurrence, safety.

Correspondence
Dr Felix Lee, Department of Upper Gastro-Intestinal Surgery, Concord Repatriation General Hospital, Hospital Rd, Concord, NSW, 2139, Australia. Email: felix.michael.lee@gmail.com

F. Lee MBBS; **O. Khoma** MD, MMed; **M. Mendu** MSLP; **G. Falk** MBBS FRACS, FACS.

Accepted for publication 12 October 2020.

doi: 10.1111/ans.16422

Abstract

Background: Paraoesophageal hernia (PEH) is often symptomatic and reduces patients' quality of life (QoL). There is ongoing debate regarding the most effective surgical technique to repair giant PEH. This study aimed to see if an elective laparoscopic non-mesh composite technique of giant PEH repair offered an advantage in symptom control, hernia recurrence, QoL, morbidity and mortality.

Methods: Data were extracted from a prospectively maintained database of patients undergoing hiatal hernia repair. Composite hernia repairs from inception for giant PEH between March 2009 and December 2015 were included. Perioperative mortality, complications, hernia recurrence rates, prevalence, recurrence of symptoms and QoL were included in analysis.

Results: Inclusion criteria were met by 218 patients. Mean age was 70 (49–93). The average hernia size was 62% (range 30–100%; SD 21). There was one perioperative death and three significant complications (Clavien–Dindo grade III and IV). Recurrence rate was 24.8%. Without recurrence, QoL improved significantly across all domains. Recurrence of hiatus hernia reduced QoL. Surgery resulted in resolution of symptoms other than dysphagia which was incompletely improved. Patients' overall satisfaction with surgery was high.

Conclusion: Composite repair of giant PEH is safe with overall good outcomes. Majority of hernia recurrence are small and asymptomatic. Hernia recurrence negatively affected long-term QoL scores.

Introduction

A giant paraoesophageal hernia (PEH) can be defined as a hernia with greater than 30% of the stomach herniating through the diaphragm.[1] These are usually type III or IV hernia and symptomatic cases generally require surgical management.[2]

PEH repairs are prone to recurrence with reported rates of up to 66%.[3,4] Attempts to reduce recurrence include the use of non-absorbable synthetic mesh repairs, Collis gastroplasty and crural release.[5,6] Mesh use has been associated with post-operative complications including oesophageal erosion, dysphagia, increased reoperative morbidity and the rare need for oesophagectomy.[7,8] The development of biologic mesh was intended to reduce complications. However, problems due to biologic mesh still occur and its benefit in reducing recurrence is only short term.[9–14] Collis gastroplasty has been used when there is insufficient oesophageal length for the repair.[15] A century has passed since the first hiatal hernia operation, yet debate regarding best technique continues. Data on quality of life (QoL) outcomes are encouraging, although concerns that recurrence negatively affects QoL exists.[14,16]

The aim of this study was to assess outcomes of composite PEH repair without mesh in a large group of patients with focus on pre-operative and post-operative symptoms, complications, recurrence and QoL. We hypothesized that the use of cardio-oesophageal junction fixation specific to composite technique had potential in improving results of PEH repair.

Methods

Data were extracted from a prospectively maintained database with the serial approval of an institutional ethics review board (CH62/6/2011-092, LNR/12/CRGH/248, CH62/6/2012-189 and

LNR/12/CRGH/246). Patients with giant PEH who underwent primary laparoscopic composite hernia repair performed between March 2009 and October 2015 were included.

The operations were performed primarily by the senior author (GF) or under direct supervision. Giant PEH was defined as 30% or more of the stomach herniating through the diaphragm based on intraoperative findings, and type III or IV.

Primary outcomes included were preoperative and post-operative symptoms, hernia recurrence and QoL.

Surgical technique

Patients were strongly encouraged to lose weight preoperatively to body mass index (BMI) <30. All procedures were laparoscopic. Principles of repair were complete reduction of hernia sac, thoracic dissection of oesophagus, vagal preservation, crural closure with deep non-absorbable sutures over sizing bougie, 360° fundoplication and cardiopexy. Detailed description of the surgical technique has been previously published.[17]

Follow-up

Patients were reviewed following surgery at 6 weeks, within the first 12 months, and then second-yearly. Self-administered QoL questionnaires were completed prior to surgery, within the first year, and then annually. The questionnaires included the Gastrointestinal Quality of Life Index (GIQOLI), dysphagia, VISICK score, DeMeester score and laryngo-pharyngeal reflux (LPR) score.[18–20] Routine endoscopy was performed within 12 months post-operatively. Where endoscopy was not possible, a barium meal was arranged.

Data management

Data were prospectively collected. Database variables included age, operation date, sex, American Society of Anesthesiologists score, BMI, preoperative symptoms, hernia size, tension at hiatal closure, post-operative symptoms, QoL and post-operative endoscopy or barium meal findings.

QoL scores were classified as either 'early', performed within 12 months of surgery, and 'late', performed later than 12 months.

SSPSS 26 (IBM, Armonk, NY, USA) was used for statistical analysis. Comparison of symptomology and association was performed with McNemar and chi-squared, Pearson's correlation and Student's *t*-test where appropriate. Comparisons of the QoL scores were done using the Student's *t*-test for those patients with paired data, and the Mann–Whitney *U*-test for unpaired data. Kruskal–Wallis analysis of variance and Student's *t*-tests were used to analyse non-parametric data. A *P*-value of <0.05 was considered statistically significant.

Results

Inclusion criteria was met by 218 patients. The average age at operation was 70 (range 44–93; SD 9.95), with 79% (n = 172) being female. Demographic characteristics are summarized in Table S1.

Operative

Successful laparoscopic composite hernia repairs were performed in 217 cases. One patient required conversion to open surgery for haemostasis of a bleeding branch from the left gastric artery.

No patients required a Collis gastroplasty in this series.

The size of hernia was estimated by the surgeon intraoperatively. The average hernia size was 62% (range 30–100%; SD 21). Patients with higher BMI tended to have smaller hiatus hernia sizes (P = 0.025).

The American Society of Anesthesiologists score was recorded for 179 patients (median 2, range 1–4).

BMI was documented in 169 patients. Mean BMI was 29 kg/m^2 (range 27–39 kg/m^2; SD 4.54); a total of 98 patients had a BMI <29 kg/m^2 and 71 had a BMI of >30 kg/m^2.

Morbidity and mortality

There was one post-operative death on day 4 due to small bowel ischaemia on a background of pre-existing atrial fibrillation, accounting for a perioperative mortality of 0.45%.

Significant complications (Clavien–Dindo grade III and above) occurred in four patients. These were an immediate hernia recurrence requiring reoperation, a mediastinal haematoma managed with drainage and antibiotics, an oesophageal injury repaired by thoracotomy and an aspiration pneumonia.

Symptoms

Patient symptoms were recorded preoperatively and at each review after surgery. Latest symptom records were used in analysis on average 30.8 months after surgery. Patient symptoms are summarized in Table 1.

Preoperative symptoms were shortness of breath (70.6%), chest pain (53.2%), heartburn (47.7%) and dysphagia (45.4%). Post-operative symptoms were dysphagia (13.8%), heartburn (3.7%) and regurgitation (3.2%).

All symptoms improved post-operatively, with the most marked improvement in shortness of breath (70.6–1.8%).

Follow-up endoscopy and barium swallow

Gastroscopy (191) or barium meal (5) was performed in 196 (89.9%) patients post-operatively between 0 and 120 months (mean 30.1 months).

Recurrence

Recurrence was graded as small (<2 cm) or large (>2 cm), and overall was 24.8% (54 patients). Small recurrences were seen in 33 patients (15.1%) and large recurrences occurred in 16 (7.3%). Recurrence size was not documented in five patients (2.3%).

Persistent symptoms were present in 26 of 54 (48.1%) patients with hernia recurrence. These included significantly higher post-operative rates of dysphagia (24.1%), heartburn (9.3%) and reflux (7.4%), compared with patients without recurrence (11.0%, 1.8% and 1.2%, respectively).

Table 1 Comparison of pre- and post-operative symptomology in patients with and without recurrence

	Patients with no recurrence (n = 164)			Patients with recurrence (n = 54)		
Symptoms	Preoperative[§] (%)	Post-operative (%)	Significance	Preoperative[§] (%)	Post-operative (%)	Significance
Heartburn	84 (51.2)	3 (1.8)[†]	0.000	20 (37)	5 (9.3)[†]	0.001
Chest pain	91 (55.5)	1 (0.6)[†]	0.000	23 (42.6)	2 (3.7)[†]	0.000
Dysphagia	73 (44.5)	18 (11)[†]	0.000	26 (48.1)	13 (24.1)[†]	0.011
Shortness of breath	115 (70.1)	2 (1.2)[†]	0.000	37 (68.5)	2 (3.7)[†]	0.000
Aspiration	18 (11)	0 (0)[†]	0.000	8 (14.8)	2 (3.7)[‡]	0.070
Regurgitation	72 (43.9)	2 (1.2)[†]	0.000	22 (40.7)	4 (7.4)[†]	0.000
Haematemesis	4 (2.4)	0 (0)[‡]	0.134	1 (1.9)	0 (0)[‡]	1.000
Malena	3 (1.8)	0 (0)[‡]	0.248	0 (0)	0 (0)[‡]	NA
Anaemia	33 (20.1)	1 (0.6)[†]	0.000	10 (18.5)	0 (0)[†]	0.004
Lethargy	20 (12.2)	2 (1.2)[†]	0.000	6 (11.1)	0 (0)[†]	0.041
Loss of weight	5 (3)	2 (1.2)[‡]	0.453	1 (1.9)	1 (1.9)[‡]	1.000
Reflux	5 (3)	2 (1.2)[‡]	0.453	1 (1.9)	4 (7.4)[‡]	0.375

[†]Statistically significant change ($P < 0.05$).

[‡]No significant difference ($P > 0.05$).

[§]Post-operative symptoms were extracted from the latest review prior to data extraction.

Univariate analysis of recurrence using chi-squared test did not significantly correlate with sex ($P = 0.60$), presence of Barrett's oesophagus ($P = 0.79$), tension at hiatal repair ($P = 0.34$) and number of hiatus repair stitches (<3 or ≥4, $P = 0.58$). Univariate analysis using Student's t-test found no significant difference with age ($P = 0.70$), BMI ($P = 0.14$) or hernia size ($P = 0.83$).

Reoperation

Reoperation was performed in 16 (7.3%) patients. The symptoms prompting reoperation included dysphagia (seven), reflux (four) and pain (one). One patient who intended for redo fundoplication was found to have oesophageal adenocarcinoma and proceeded to oesophagectomy. Other indications for revision surgery included stitch breakdown, oesophageal injury repair requiring thoracotomy and acute gastric compromise from recurrence. One patient did not have their reason for reoperation available. Amongst patients proceeding to revision surgery, 10 patients had proven recurrence at the time of operation.

Barrett's oesophagus

Barrett's oesophagus was present 39.8% (76/191) of patients with endoscopic follow-up. The frequency of Barrett's oesophagus was similar between patients with recurrence (33.3%) and those without (35.4%).

Quality of life

Completion of QoL questionnaires was approximately 40%. Preoperative QoL was reduced in patients with giant PEH when compared to a perfect score. Significant improvement was reported in early and late post-operative review in patients without recurrence across all self-reported data. Patients with hernia recurrence had significant improvement in GIQOLI, VISIK and DeMeester scores on early follow-up; however, this was not sustained during late follow-up. Overall satisfaction was 90%. QoL data are summarized in Table 2.

Discussion

Giant PEH can cause debilitating symptoms and significant complications. It is accompanied by mortality rates of up to 16.4% over 4 years.[2] Therefore, it is prudent that symptomatic giant PEH be repaired when encountered given appropriate balance of risk.

The demographics of the patient cohort is consistent with other studies with a female predominance and advanced age.[3,21,22] Despite age often being perceived as a barrier to surgery, there is contrary evidence suggesting appropriately selected operative management is as safe and effective in the elderly as in younger patients.[23] Regardless of age, repair of PEH in elective setting is safer than emergency surgery for complicated PEH. An American nationwide analysis of 23 514 patients undergoing repair of complicated (strangulated, incarcerated or obstructed) PEH found a mortality rate of 5.3% compared to 1.02% in elective cases.[24] In this series, no post-operative patient suffered acute hernia-related complication.

Giant PEH are known to cause dyspnoea by cardiac inflow obstruction which improves following hernia repair.[25] This study showed markedly reduced post-operative rates of dyspnoea and all other symptoms apart from dysphagia, which improved to a lesser degree. Post-operative dysphagia was significantly more common in patients with recurrence (24% versus 11%, $P = 0.024$).

Rates of recurrence reported in literature vary between 8% and 66%.[3,26] This is partly due to the use of different definitions of recurrence.[21,22,26,27] The rate of anatomical recurrence in this group is likely to be accurate as 88% of patients were followed up endoscopically or radiologically and all recurrences were reported regardless of size.

Currently, none of the various techniques of large PEH repair have proved to be superior.[12–14,28] A recent randomized controlled study suggests that there was no discernible difference between clinical outcomes of patients undergoing giant PEH repair with either sutures alone, absorbable and non-absorbable mesh at 1, 3, 6 and 12 months.[13] Furthermore, the same study found in 2019 that the use of absorbable mesh may result in worse symptomatic outcomes 5 years after surgery.[12] Utilization of either mesh was not

Table 2 Summary of self-reported QoL

	Patients without hernia recurrence			Patients with hernia recurrence		
	Preoperative (n = 93)	Early follow-up (n = 114)	Late follow-up (n = 114)	Preoperative (n = 27)	Early follow-up (n = 30)	Late follow-up (n = 30)
GIQOLI	90.46 (SD 23.48)	109.75 (SD 19.65)†	107.16 (SD 21.04)†	91.37 (SD 21.8)	104.65 (SD 21.82)‡	96.27 (SD 26.69)§
VISIK	2.96 (SD 0.99)	1.89 (SD 0.88)†	1.92 (SD 0.84)†	2.93 (SD 0.96)	2.13 (SD 0.82)¶	2.43 (SD 0.86)†
Dysphagia	35.73 (SD 9.2)	38.05 (SD 7.39)§	37.48 (SD 8.24)§	37.22 (SD 8.3)	33.08 (SD 10.55)§	35.33 (SD 9.82)§
DeMeester score	6.89 (SD 3.18)	3.66 (SD 3.23)†	3.71 (SD 3.33)†	6.85 (SD 3.44)	4.37 (SD 3.39)¶	5.77 (SD 3.12)§
LPR score	17.12 (SD 11.24)	9.23 (SD 9.56)†	10.75 (SD 9.92)†	17.74 (SD 12.9)	11.63 (SD 10.83)§	12.87 (SD 10.16)§
Overall satisfaction with surgery		96.5% satisfied 3.5% not satisfied	93.9% satisfied 6.1% not satisfied		93.3% satisfied 6.7% not satisfied	90% satisfied 10% not satisfied

†Statistically significant improvement ($P < 0.00$).

‡Statistically significant improvement ($P = 0.04$).

§No significant difference ($P > 0.05$).

¶Statistically significant improvement ($P < 0.01$).

GIQOLI, Gastrointestinal Quality of Life; LPR, laryngo-pharyngeal reflux; QoL, quality of life.

shown to improve symptom control or QoL.[12] The results of this study demonstrated fair symptom control, recurrence and reoperation rates comparable to other techniques.

Within this series, there were no patients who required a Collis gastroplasty to achieve an appropriate repair with sufficient oesophageal length. Low rates of short oesophagus may be partially explained by widespread use of proton pump inhibitors, and was seen previously in strictural disease and scarred oesophagus.[15] This is not commonly the situation in PEH where the oesophagus is relatively elastic. The fact that results in this study, without gastroplasty, are similar to other techniques supports this view.

Median time to recurrence diagnosis was 22.5 months (range 2–99 months, mean 30.5 months), which is within the range reported for suture, synthetic and biologic mesh repairs.[21,22,29,30] Median time to recurrence in this group corresponded with time of worsening of QoL scores in patients with recurrence. However, without more frequent reviews, relationship of symptoms and recurrence could only be approximate.

Studies of hernia recurrence have yet to provide a predictive framework. Previous works indicated hiatus size, or volume may predict recurrence.[31,32] Others have found factors such as hernia characteristics, age, BMI, gender, race and smoking status do not predict hernia recurrence rates.[4,33,34] Our results support the latter.

Reoperation rates were low (7%), which is similar to previous reports.[21,29] Revision surgery was offered to patients with severe persistent symptoms resistant to medical treatment. More patients with larger recurrences (33%) underwent reoperation compared to those with smaller recurrences (9.1%).

Hernia recurrence was not associated with significant improvement in GIQOLI scores on late follow-up. Previous studies linked recurrence to impairment in QoL scores at 6 months post-operatively. This is the first study to correlate recurrence with negative QoL outcome on follow-up after 2 years. QoL scores showed improvement after surgery ($P = 0.04$), but in the late recurrence assessment this improvement had deteriorated to be insignificant.

However, overall satisfaction with surgery was high (90%) and independent of post-operative anatomical hernia recurrence as has been evident for many years. GIQOLI did not capture improvements in respiratory function post-operatively understating QoL improvement relating to dyspnoea. LPR scores are somewhat reflective of respiratory symptoms that may be precipitated by proximal regurgitation events irritating the laryngo-pharynx.[35] Significant improvement in LPR scores was demonstrated on early and late follow-up.

Dysphagia is a common post-operative symptom in patients undergoing fundoplication. Some studies suggested that a 360° fundoplication was associated with more frequent dysphagia than partial fundoplication.[36] In this cohort, close to 45% of patients complained of dysphagia preoperatively compared to 10% post-operatively.

Barrett's oesophagus was commonly encountered (34.9%). This is a high frequency and patients may be at risk of neoplasia. There is indication for perioperative endoscopy to trigger surveillance. In this group, there was no increased recurrence in patients with Barrett's as previously reported.[37]

Strengths of the study include the single surgeon database, surgery performed in a high-volume centre, prospectively collected data, thorough record of symptoms and use of self-administered QoL and satisfaction surveys. Limitations of the study include variable lengths of follow-up, retrospective data analysis, poor sensitivity of GIQOLI to dyspnoea, single surgeon subjective assessment of hernia size and a non-generalizable cohort design.

Conclusion

Laparoscopic composite repair of giant PEH is a safe and effective method associated with high patient satisfaction. Outcomes and recurrence rates are comparable to other published techniques. Hernia recurrence negatively affected long-term self-reported QoL scores, underscoring the desirability of continued efforts to improve recurrence rates.

Author Contributions

Felix Lee: Data curation; formal analysis; investigation; methodology; software; writing-original draft; writing-review and editing.

Conceptualization; formal analysis; investigation; methodology; software; supervision; writing-original draft; writing-review and editing. **Maite Mendu:** Data curation; software. Conceptualization; data curation; formal analysis; investigation; methodology; resources; supervision; validation; visualization; writing-review and editing.

Conflicts of interest

None declared.

References

1. Mitiek MO, Andrade RS. Giant hiatal hernia. *Ann. Thorac. Surg.* 2010; **89**: S2168–73.
2. Sihvo EI, Salo JA, Rasanen JV, Rantanen TK. Fatal complications of adult paraesophageal hernia: a population-based study. *J. Thorac. Cardiovasc. Surg.* 2009; **137**: 419–24.
3. Dallemagne B, Kohnen L, Perretta S, Weerts J, Markiewicz S, Jehaes C. Laparoscopic repair of paraesophageal hernia. Long-term follow-up reveals good clinical outcome despite high radiological recurrence rate. *Ann. Surg.* 2011; **253**: 291–6.
4. Hashemi M, Peters JH, DeMeester TR *et al.* Laparoscopic repair of large type III hiatal hernia: objective followup reveals high recurrence rate. *J. Am. Coll. Surg.* 2000; **190**: 553–60.
5. Kuster GG, Gilroy S. Laparoscopic technique for repair of paraesophageal hiatal hernias. *J. Laparoendosc. Surg.* 1993; **3**: 331–8.
6. Greene CL, DeMeester SR, Zehetner J, Worrell SG, Oh DS, Hagen JA. Diaphragmatic relaxing incisions during laparoscopic paraesophageal hernia repair. *Surg. Endosc.* 2013; **27**: 4532–8.
7. Frantzides CT, Carlson MA, Loizides S *et al.* Hiatal hernia repair with mesh: a survey of SAGES members. *Surg. Endosc.* 2010; **24**: 1017–24.
8. Parker M, Bowers SP, Bray JM *et al.* Hiatal mesh is associated with major resection at revisional operation. *Surg. Endosc.* 2010; **24**: 3095–101.
9. Stadlhuber RJ, Sherif AE, Mittal SK *et al.* Mesh complications after prosthetic reinforcement of hiatal closure: a 28-case series. *Surg. Endosc.* 2009; **23**: 1219–26.
10. Oelschlager BK, Pellegrini CA, Hunter J *et al.* Biologic prosthesis reduces recurrence after laparoscopic paraesophageal hernia repair: a multicenter, prospective, randomized trial. *Ann. Surg.* 2006; **244**: 481–90.
11. Oelschlager BK, Pellegrini CA, Hunter JG *et al.* Biologic prosthesis to prevent recurrence after laparoscopic paraesophageal hernia repair: long-term follow-up from a multicenter, prospective, randomized trial. *J. Am. Coll. Surg.* 2011; **213**: 461–8.
12. Watson DI, Thompson SK, Devitt PG *et al.* Five year follow-up of a randomized controlled trial of laparoscopic repair of very large hiatus hernia with sutures versus absorbable versus nonabsorbable mesh. *Ann. Surg.* 2019; **272**: 241–247.
13. Watson DI, Thompson SK, Devitt PG *et al.* Laparoscopic repair of very large hiatus hernia with sutures versus absorbable mesh versus non-absorbable mesh: a randomized controlled trial. *Ann. Surg.* 2015; **261**: 282–9.
14. Zhang C, Liu D, Li F *et al.* Systematic review and meta-analysis of laparoscopic mesh versus suture repair of hiatus hernia: objective and subjective outcomes. *Surg. Endosc.* 2017; **31**: 4913–22.
15. Collis JL. An operation for hiatus hernia with short oesophagus. *Thorax* 1957; **12**: 181–8.
16. Koetje JH, Irvine T, Thompson SK *et al.* Quality of life following repair of large hiatal hernia is improved but not influenced by use of mesh: results from a randomized controlled trial. *World J. Surg.* 2015; **39**: 1465–73.
17. D'Netto TJ, Falk GL. A technique for the laparoscopic repair of paraoesophageal hernia without mesh. *J. Gastrointest. Surg.* 2014; **18**: 851–7.
18. DeMeester TR, Johnson LF. The evaluation of objective measurements of gastroesophageal reflux and their contribution to patient management. *Surg. Clin. North Am.* 1976; **56**: 39–53.
19. Eypasch E, Williams JI, Wood-Dauphinee S *et al.* Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. *Br. J. Surg.* 1995; **82**: 216–22.
20. Visick AH. A study of the failures after gastrectomy. *Ann. R. Coll. Surg. Engl.* 1948; **3**: 266–84.
21. Le Page PA, Furtado R, Hayward M *et al.* Durability of giant hiatus hernia repair in 455 patients over 20 years. *Ann. R. Coll. Surg. Engl.* 2015; **97**: 188–93.
22. Luketich JD, Nason KS, Christie NA *et al.* Outcomes after a decade of laparoscopic giant paraesophageal hernia repair. *J. Thorac. Cardiovasc. Surg.* 2010; **139**: 395–404.
23. Khoma O, Mugino M, Falk GL. Is repairing giant hiatal hernia in patients over 80 worth the risk? *Surgeon* 2020; **18**: 197–201.
24. Fullum TM, Oyetunji TA, Ortega G *et al.* Open versus laparoscopic hiatal hernia repair. *JSLS.* 2013; **17**: 23–9.
25. Naoum C, Falk GL, Ng AC *et al.* Left atrial compression and the mechanism of exercise impairment in patients with a large hiatal hernia. *J. Am. Coll. Cardiol.* 2011; **58**: 1624–34.
26. Quinn MA, Geraghty AJ, Robertson AGN, Paterson-Brown S, Lamb PJ; Edinburgh Oesophago-Gastric Surgery Group. Long-term outcomes following surgical repair of giant paraoesophageal hiatus hernia. *Surg. Endosc.* 2019; **33**: 1846–53.
27. Diaz S, Brunt LM, Klingensmith ME, Frisella PM, Soper NJ. Laparoscopic paraesophageal hernia repair, a challenging operation: medium-term outcome of 116 patients. *J. Gastrointest. Surg.* 2003; **7**: 59–67.
28. Tam V, Winger DG, Nason KS. A systematic review and meta-analysis of mesh vs suture cruroplasty in laparoscopic large hiatal hernia repair. *Am. J. Surg.* 2016; **211**: 226–38.
29. Furtado RV, Vivian SJ, van der Wall H, Falk GL. Medium-term durability of giant hiatus hernia repair without mesh. *Ann. R. Coll. Surg. Engl.* 2016; **98**: 450–5.
30. Tam V, Luketich JD, Levy RM *et al.* Mesh cruroplasty in laparoscopic repair of paraesophageal hernias is not associated with better long-term outcomes compared to primary repair. *Am. J. Surg.* 2017; **214**: 651–6.
31. Grubnik VV, Malynovskyy AV. Laparoscopic repair of hiatal hernias: new classification supported by long-term results. *Surg. Endosc.* 2013; **27**: 4337–46.
32. Jones R, Simorov A, Lomelin D, Tadaki C, Oleynikov D. Long-term outcomes of radiologic recurrence after paraesophageal hernia repair with mesh. *Surg. Endosc.* 2015; **29**: 425–30.
33. Armijo PR, Pokala B, Misfeldt M, Pagkratis S, Oleynikov D. Predictors of hiatal hernia recurrence after laparoscopic anti-reflux surgery with hiatal hernia repair: a prospective database analysis. *J. Gastrointest. Surg.* 2019; **23**: 696–701.
34. El Lakis MA, Kaplan SJ, Hubka M, Mohiuddin K, Low DE. The importance of age on short-term outcomes associated with repair of giant paraesophageal hernias. *Ann. Thorac. Surg.* 2017; **103**: 1700–9.
35. Khoma O, Burton L, Falk MG, Van der Wall H, Falk GL. Predictors of reflux aspiration and laryngo-pharyngeal reflux. *Esophagus.* 2020; **17**: 355–62.

36. Hajibandeh S, Hajibandeh S, Pugh M *et al*. Impact of Toupet versus Nissen fundoplication on dysphagia in patients with gastroesophageal reflux disease and associated preoperative esophageal dysmotility: a systematic review and meta-analysis. *Surg. Innov.* 2018; **25**: 636–644.
37. Miholic J, Hafez J, Lenglinger J *et al*. Hiatal hernia, Barrett's esophagus, and long-term symptom control after laparoscopic fundoplication for gastroesophageal reflux. *Surg. Endosc.* 2012; **26**: 3225–31.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Patient characteristics, hernia size and complications.

THE SURGEON 18 (2020) 197–201

Is repairing giant hiatal hernia in patients over 80 worth the risk?

Oleksandr Khoma [a,d,*], *Miho Mugino* [a], *Gregory L. Falk* [b,c]

[a] *Department of Upper Gastro-Intestinal Surgery, Concord Repatriation General Hospital. Hospital Road, Concord, NSW, 2137, Australia*
[b] *Concord Repatriation General Hospital, Sydney, Australia*
[c] *University of Sydney, 29/12-18 Tryon Road, Lindfield, NSW, 2070, Australia*
[d] *School of Medicine, University of Notre Dame Australia, Sydney, NSW, Australia*

ARTICLE INFO

Article history:
Received 31 August 2018
Received in revised form
12 September 2019
Accepted 14 September 2019
Available online 18 October 2019

Keywords:
Hiatal hernia
Laparoscopic surgery
Elderly
Quality of life

ABSTRACT

Patients with giant hiatal hernia (GHH) are often symptomatic and have significantly reduced quality of life (QoL). Advanced age is a predictor of increased morbidity and mortality in open hiatal surgery, however, outcomes of laparoscopic surgery in patients over the age of 80 are limited to case reports and small case series.

Data was extracted from a prospectively maintained database. Consecutive patients over the age of 80 with GHH that have undergone surgery were included. Peri-operative mortality, complications, recurrence rates, use of acid suppressive medication and QoL was analysed. Search of Ryerson index was performed to determined post-operative survival.

Inclusion criteria were met by 89 patients. Mean age was 84 (80–93). The mean volume of herniated stomach was 70.9% range 30–100%; SD 27.25). There was one death in this cohort on day 30 from myocardial infarction and one mediastinal collection requiring percutaneous radiological drainage and antibiotics. There were no other major complications (Clavien-Dindo Grade III-IV). Mean post-operative survival was 74.5 months (SD 47.8). GIQLI was reduced pre-operatively (mean 91.8; SD 19.4). There was significant improvement in GIQLI scores at early (mean 101.45; SD 21.2) and late (mean 106.7; SD 19.2) post-operative follow-up ($p = 0.005$). Pre-operative Visick scores (mean 2.92; SD 0.98) have improved significantly in early (mean 1.94; SD 0.97; $p = 0.000$) and late (mean 2.03; SD 0.99; $p = 0.001$) post-operative periods. Satisfaction with surgery was 97% during early and 93.3% during late post-operative follow up.

Laparoscopic repair of GHH in appropriately selected elderly patients is safe and results in significant improvement in quality of life.

Introduction

Symptomatic giant hiatal hernia (GHH) is one of the indications for laparoscopic hiatal hernia repair. Giant hiatal hernia is usually defined as hernia containing greater than 30 percent of the stomach, although some authors consider herniae greater than 50 percent as GHH.[1] Various techniques of hiatal hernia repair have been described, usually combined with an anti-reflux procedure such as Nissen, Toupet or Dor fundoplication with or without Collis gastroplasty.[2] Surgical management of asymptomatic GHH remains a subject of a debate. One of the largest series reported 3.5-fold increase in mortality in emergency GHH repair compared to elective procedures.[2] Other data, however, suggests that the need for an emergency operation in elderly patient with a GGH

This research article was presented at the International Society for Diseases of the Esophagus (ISDE) in September 2018. Abstract was subsequently published in Diseases of the Esophagus journal (official ISDE journal). Full text of this paper has not been previously published and is not submitted for publication for any other journals.

* *Corresponding author*. 29/12-18 Tryon Road, Lindfield 2070, Australia. Fax: +612 9416 2907.
E-mail address: khoma.a@gmail.com (O. Khoma).

https://doi.org/10.1016/j.surge.2019.09.004

decreases with age, adding further confusion to how best manage these patients.[3–5] Advanced age was historically considered to be a contraindication for elective GHH surgery, however, recent studies have shown that age alone is not an absolute contraindication.[6] Majority of published literature defines "advanced" age as being above 65 years old. With increase in life expectancy in the last 30 years and improved management of chronic illnesses, it is perhaps time to re-evaluate the definition of "advanced" age for surgical purposes.[7]

A number of studies examined outcomes of laparoscopic fundoplication in elderly patients.[3,4,8,9] The majority of the published studies report similar outcomes of laparoscopic fundoplication between the elderly and younger patients. Most series include all size herniae, however, very few specifically address patients with GHH.

In recent years, multiple studies investigated the effect of advanced age on surgical outcomes unsurprisingly showing that morbidity and mortality increases with advanced age.[10,11] Clinicians treating aging population, especially in developed countries, are often faced with dilemma of potential surgery in patients of advanced age.

To date, published data on outcomes of laparoscopic fundoplication in patients over 80 years old is limited to case reports and small case series.[12,13] Other larger series are limited by the fact that majority of the patients had open surgery.[14]

The purpose of this study was to examine outcomes of laparoscopic repair of GHH in a large group of symptomatic patients over the age of 80 with focus on safety, life expectancy and effects of surgery on quality of life.

Patients and methods

Data was extracted from a prospectively maintained single-surgeon database of laparoscopic fundoplication procedures between 1995 and 2014. Ethics approval for the study was provided by the Concord Hospital Ethics Committee (LNR/12 CRGH/248). This study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided informed written consent to participate in research. Consecutive patients who were operated for GHH (>30% of stomach in the chest) aged 80 or older at the time of surgery were included.

Symptomatic patients with GHH that were assessed as medically fit to undergo surgery were offered surgery. None of the patients in this cohort were previously declined to undergo surgery in our centre, in other words, there was no patients in this cohort that we were "observing" who developed more acute symptoms necessitating emergency operation.

Patients were evaluated prior surgery for cardiac, respiratory and renal disease as well as assessed for activities of daily living capability. Patients with dyspnoea underwent stress echocardiogram and patients with evidence of significant vascular disease were offered carotid duplex scanning. Multiple specialty optimization was pursued, and anaesthetic pre-operative evaluation undertaken.

All patients had undergone hiatal hernia repair without mesh. Principles of repair were complete reduction and excision of hernia sac, adequate mobilization of oesophagus, anterior and posterior crural closure with non-absorbable sutures, 360-degree fundoplication and cardiopexy. Manometry was not routinely performed in this group of patients pre-operatively. Loose 360-degree fundoplication was performed on all patients together with cardiopexy to prevent re-herniation. Details of the operative technique were previously published by the senior author.[15]

Operation details, peri-operative mortality, complications, recurrence of hernia, recurrence of symptoms, need for acid suppression medication and quality of life data were analysed.

Quality of life (QOL) data was collected pre-operatively, in early post-operative period (within 12 months) and later post-operative period (24 months or later). QOL data included gastro-intestinal quality of life index (GIQLI), modified Visick score, dysphagia score and overall satisfaction with surgery.

Ryerson index is Australian online registry of death and funeral notices (http://ryersonindex.org). A search of Ryerson index was conducted using patients' names, dates of birth (age) and places of residence. Listed dates of death/funeral were used to establish time from the operation to the time of death for the patients that have passed away.

Statistical analysis was performed using SPSS Statistics 23 software (IBM, New York, United States). Results with p value of 0.05 or less were considered significant.

Results

Inclusion criteria were met by 89 patients (20 male and 69 female). Average age at the time of surgery was 84 (80–93).

Most common pre-operative symptoms were early satiety, dyspnoea and chest pain. Tables 1–3.

Laparoscopic fundoplication was successful in 86 patients, including two patients who had previous hernia repair (revision operation). Three patients had an open procedure. Collis gastroplasty was performed in three of the cases to assist positioning of the tension free subdiaphragmatic wrap in patients with short oesophagus. One of the patients having open surgery had previous hiatal repair with recurrent hernia (re-do operation), there was one conversion from laparoscopic to open procedure due to short oesophagus and very friable gastric tissue secondary to chronic intrathoracic gastric volvulus, and third patient having upfront open surgery had previous colectomy and was expected to have significant adhesions. No difference in measured outcomes was demonstrated between patients that underwent open compared to laparoscopic GHH repair.

Table 1 – Patient characteristics, complications and survival.

	male	female
Number of patients	20	69
Age average (range)	84 (80–90)	84.1 (80–93)
Size of the hernia (% of the stomach; average/range)	63.5 (30–100)	73 (30–100)
Complications major/minor	0/2	1 (death)/1
Post-operative survival Average (range)	66.8 (6–233)	76.9 (1–180)

Table 2 – Prevalence of symptoms of GHH.

Symptom	N	%
early satiety	63	70.9%
dyspnoea	56	62.9%
chest pain	48	53.9%
dysphagia	44	49.4%
heartburn	20	22.5%
weight loss	17	19.1%
UGI bleeding or anaemia	9	10.1%
vomiting	7	7.9%
cough	4	4.5%
anorexia	3	3.3%
complete anorexia	3	3.3%
presyncope	2	2.3%

In this cohort 3 patients had previous hiatal hernia repair with recurrence. Average time to recurrence from the original operation was 10 years. One of the "re-do" operations was done as a primary open procedure, whilst the other two were performed laparoscopically.

Reported percentage of herniated stomach is estimated by the operating surgeon and recorded in operation report. This usually corresponded to pre-operative imaging (Barium swallow). The proportion of herniated stomach was 70.9% on average (range 30–100%; SD 27.25), the hiatal defect was large in all patients. Hernia contained >50% of the stomach in 76.4% of the patients. Chronic intrathoracic gastric volvulus was found in 13 patients (14.6%) at the time of surgery. 11 patients had type IV hernia most commonly containing entire stomach as well as transverse colon and greater omentum, remaining patients had type III hernia (see Fig. 1).

There was 1 readmission at post-operative day 30 with myocardial infarction which unfortunately resulted in patient's death. One patient developed post-operative mediastinal collection (infected hematoma) which was managed with percutaneous drainage and intravenous antibiotics. There were no other major complications (Clavien-Dindo Grade III-IV). Three patients in this cohort developed port site wound infections and were treated with oral antibiotic for an average of 7 days (Clavien-Dindo Grade II). It is likely that many of the minor complications are underreported as patients are usually discharged on post-operative day 3 and minor complications treated by the primary care physicians may be missing from our records.

Patients were routinely followed up at 2, 6, 12 and 24 months and on as required bases thereafter. Follow up included assessment of ongoing symptoms by an experienced upper GI surgeon, QoL questionnaire and an endoscopy. It is our protocol to routinely perform endoscopy in the first 12 months post operatively to check for oesophagitis as well as early recurrence. Previous reports by our group indicated up to 28% incidence of Barrett's oesophagus following hiatal hernia repair.[16]

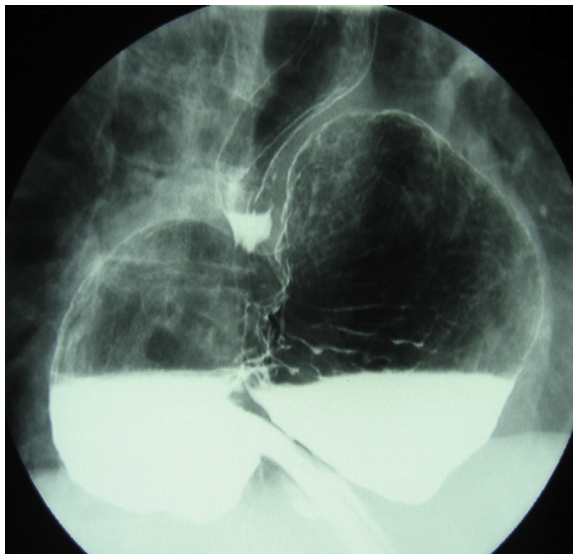


Fig. 1 – Barium meal showing giant hiatal hernia with intrathoracic gastric volvulus. Entire stomach is above the diaphragm.

Post-operative endoscopy was performed for 28 patients within 12 months of surgery. Hernia recurrence was found in 6 patients. Size of recurrence in all patients was small (1–3 cm). Endoscopy was not performed in high risk patients, as well as in patients who refused the procedure. Barium meals were performed in cases when patients continued to experience post-operative symptoms (usually dysphagia or reflux) with no apparent cause on endoscopy.

The search of Ryerson index (online database of death and funeral notices) confirmed that 44 patients in this cohort died distant from surgery. Post-operative survival was on average of 74.5 months (SD 47.8; range 1–233).

Quality of life information was available for 26 patients pre-operatively, 33 patients on early and 30 on late post-operative follow up. Quality of life data collection in this cohort has proven difficult pre-operatively and during follow up. All of the patients were issued with quality of life questionnaires and return envelopes, however, only a third complied. Some of the obstacles to QoL completion pre-

Table 3 – Quality of Life summary.

	Pre-op (n = 26)	Early follow up (n = 33)	Late follow up (n = 30)
GIQOL	91.77 (SD 19.385)	101.45 (SD 21.194)	106.733 (SD 19.213)[a]
VISIK	2.92 (SD 0.98)	1.94 (SD 0.97)[a]	2.03 (SD 1)[a]
Dysphagia	9.52 (SD 10.05)	7.57 (SD 9.51)	7.16 (SD 9.35)
Overall satisfaction	n/a	97% (72.7 %very satisfied)	93.3% (73.3% very satisfied)
PPI use	73.1%	42.4%	46.7%

[a] Indicates statistically significant improvement.

operatively were poor physical and/or cognitive state, language barrier and short period of time between initial review and operation. Patients in this study included state-wide referrals (NSW, Australia), long distances and remote residence being another barrier to follow up.

GIQLI was reduced pre-operatively (mean 91.8; SD 19.4). There was improvement in GIQLI scores on early (mean 101.45; SD 21.2) and late (mean 106.7; SD 19.2) post-operative follow up. Improvement in GIQLI was statistically significant during late follow up (t-test; $p = 0.005$). Pre-operative Visick scores (mean 2.92; SD 0.98) improved significantly in early (mean 1.94; SD 0.97; t-test $p = 0.000$) and late (mean 2.03; SD 0.99; t-test $p = 0.001$) post-operative periods. Dysphagia scores were high pre-operatively (mean 9.5; SD 10). There was a modest improvement in dysphagia score in early (mean 7.6; SD 9.5) and late (mean 7.2; SD 9.4) post-operative periods. Improvements in dysphagia scores were not statistically significant.

During early post-operative follow up 97% of the patients were satisfied with overall outcome of their operation, whilst 3% were dissatisfied. Overall satisfaction scores remained high on late follow up (93.3% satisfied, 6.7% dissatisfied).

The majority of patients (73.1%) were prescribed anti-acid medication before surgery, most commonly proton-pump inhibitors (PPI). Although some patients no longer required medication after surgery, 42.4% of patients in early and 46.7% in late post-operative period remained on PPI. Appropriateness of prescription could not be evaluated.

Most importantly, no patient developed acute complications of GHH (i.e. acute intrathoracic gastric volvulus or ischemia) following surgery.

Discussion

GHH can cause significant symptoms (early satiety, dysphagia, dyspnoea, retrosternal pain, bloating and heartburn) and reduce quality of life.[1] Each year an estimated 1.1% of asymptomatic patients will develop a complication requiring emergency surgery,[5] this number may higher in patients with GHH. Sihvo et al. reported mortality of 16.4% over 4 years in patients with symptomatic GHH managed non-operatively.[17]

Laparoscopic surgery has proven sustained benefits in improving symptoms and quality of life in patients with symptomatic GHH.[16] Patients are most commonly diagnosed with hiatal hernia in the seventh and eighth decades of life.[5] Despite surgery being safe and improving quality of life, many symptomatic patients are not considered for a surgical opinion because of advanced age and perceived frailty.[5,10,11]

Higashi et al. have shown good outcomes of laparoscopic anterior gastroplexy in a group of 8 patients with median age of 82 years (74–87).[12] Our study is the first report of its kind in a large group where all patients undergone hiatal hernia repair and were greater than 80 years old.

Recent large studies have confirmed that elderly patients undergoing any surgery are at higher risk of complications and death.[18] Story at al. showed that having an emergency operation had a similar odds ratio (OR) for mortality and major complications to being 80–89 years old.[18] Study by Fullum et al. showed that age over 80 was the strongest predictor of mortality in patients undergoing GHH repair.[19]

In our group of elderly patients, surgery has shown to be safe. Mortality in this cohort (1.12%) is similar to that reported with elective GHH surgery (1.4%) in the non-geriatric population.[5] Significant improvement in quality of life and Visick scores were sustained at 2 year follow up. Average post-operative survival was close to 6 years, which is a significant benefit. Moreover, none of the patients have died as a consequence of complication of GHH after surgery, very different from the non-operative experience.

As cardiorespiratory fitness declines with age, repair of giant hiatal hernia offers benefit by improving lung volume and reducing cardiac inflow obstruction by the hernia, and consequent improvement in exercise capability.[20]

Improvement in dysphagia scores post-operatively was an encouraging finding in this group. Further studies are needed to assess the effect of improvement in dysphagia and GIQLI on nutritional status of elderly patients.

This study demonstrates that in elderly patients repair of giant hiatal hernia is safe, eliminates the risks of acute complications of GHH and significantly improves quality of life. The findings of this study may shift risk to benefit balance to reassure anaesthetists and referring physicians that age alone should not prevent consideration of surgery.

Moreover, another study by our group has shown that GHH can cause cardiac inflow obstruction, manifesting as left atrial compression with poor exercise tolerance and post-prandial pre-syncope.[20] Cardio-respiratory status of patients with giant hiatal herniae improves once hernia is reduced and cardiac inflow obstruction is relieved.

Life expectancy in Australia as in many other countries continues to rise. Increasing number of patients will be diagnosed with GHH at a very advanced age. Surgical management in a specialized tertiary centre with experience in GHH in elderly appears to be safe and feasible. This study demonstrates that age alone should not be a limiting factor when considering surgery for GHH in patients of advanced age.

The limitations of this study are retrospective analysis of prospectively collected data, cohort design and significant gaps in quality of life data.

Funding

No funding was received towards this research.

Conclusion

Appropriate elderly patients with symptomatic GHH benefit from surgery which is safe and results in improved quality of life.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.surge.2019.09.004.

REFERENCES

1. Mitiek MO, Andrade RS. Giant hiatal hernia. *Ann Thorac Surg* 2010;**89**(6):S2168–73.
2. Luketich JD. *Master techniques in surgery: esophageal surgery*. Wolters Kluwer Health; 2014.
3. Compagna R, Rispoli C, Rocco N, Braun A, Avallone U, Amato B. Laparoscopic antireflux surgery in the elderly. *BMC Geriatr* 2009;**9**(Suppl 1). A29-A.
4. Cowgill SM, Arnaoutakis D, Villadolid D, Al-Saadi S, Arnaoutakis D, Molloy DL, et al. Results after laparoscopic fundoplication: does age matter? *Am Surg* 2006;**72**(9):778–83. discussion 83-4.
5. Stylopoulos N, Gazelle GS, Rattner DW. Paraesophageal hernias: operation or observation? *Ann Surg* 2002;**236**(4):492–500. discussion -1.
6. Fei L, Rossetti G, Moccia F, Marra T, Guadagno P, Docimo L, et al. Is the advanced age a contraindication to GERD laparoscopic surgery? Results of a long term follow-up. *BMC Surg* 2013;**13**(Suppl 2):S13.
7. Christensen K, Doblhammer G, Rau R, Vaupel JW. Ageing populations: the challenges ahead. *Lancet* 2009;**374**(9696):1196–208.
8. Trus TL, Laycock WS, Wo JM, Waring JP, Branum GD, Mauren SJ, et al. Laparoscopic antireflux surgery in the elderly. *Am J Gastroenterol* 1998;**93**(3):351–3.
9. Tolone S, Docimo G, Del Genio G, Brusciano L, Verde I, Gili S, et al. Long term quality of life after laparoscopic antireflux surgery for the elderly. *BMC Surg* 2013;**13**(Suppl 2):S10.
10. Brown NA, Zenilman ME. The impact of frailty in the elderly on the outcome of surgery in the aged. *Adv Surg* 2010;**44**:229–49.
11. Partridge JS, Harari D, Dhesi JK. Frailty in the older surgical patient: a review. *Age Ageing* 2012;**41**(2):142–7.
12. Higashi S, Nakajima K, Tanaka K, Miyazaki Y, Makino T, Takahashi T, et al. Laparoscopic anterior gastropexy for type III/IV hiatal hernia in elderly patients. *Surg Case Rep* 2017;**3**:45.
13. Wongrakpanich S, Hassidim H, Chaiwatcharayut W, Manatsathit W. A case of giant hiatal hernia in an elderly patient: when stomach, duodenum, colon, and pancreas slide into thorax. *J Clin Gerontol Geriatr* 2016;**7**(3):112–4.
14. El Lakis MA, Kaplan SJ, Hubka M, Mohiuddin K, Low DE. The importance of age on short-term outcomes associated with repair of giant paraesophageal hernias. *Ann Thorac Surg* 2017;**103**(6):1700–9.
15. D'Netto TJ, Falk GL. A technique for the laparoscopic repair of paraoesophageal hernia without mesh. *J Gastrointest Surg : Off J Soc Surg Aliment Tract* 2014;**18**(4):851–7. discussion 7.
16. Page PL, Furtado R, Hayward M, Law S, Tan A, Vivian S, et al. Durability of giant hiatus hernia repair in 455 patients over 20 years. *Ann R Coll Surg Engl* 2015;**97**(3):188–93.
17. Sihvo EI, Salo JA, Rasanen JV, Rantanen TK. Fatal complications of adult paraesophageal hernia: a population-based study. *J Thorac Cardiovasc Surg* 2009;**137**(2):419–24.
18. Story DA, Leslie K, Myles PS, Fink M, Poustie SJ, Forbes A, et al. Complications and mortality in older surgical patients in Australia and New Zealand (the REASON study): a multicentre, prospective, observational study. *Anaesthesia* 2010;**65**(10):1022–30.
19. Fullum TM, Oyetunji TA, Ortega G, Tran DD, Woods IM, Obayomi-Davies O, et al. Open versus laparoscopic hiatal hernia repair. *Jsls* 2013;**17**(1):23–9.
20. Naoum C, Falk GL, Ng AC, Lu T, Ridley L, Ing AJ, et al. Left atrial compression and the mechanism of exercise impairment in patients with a large hiatal hernia. *J Am Coll Cardiol* 2011;**58**(15):1624–34.

original article

Eur Surg (2020) 52:277–281
https://doi.org/10.1007/s10353-020-00652-1

european surgery
ACA Acta Chirurgica Austriaca

Is fundoplication advisable in repair of para-oesophageal hernia? “Little operation” or “big operation”?

Gregory L. Falk · Leigh Archer · Suzanna C. Gooley

Received: 20 January 2020 / Accepted: 2 July 2020 / Published online: 24 July 2020

Summary
Background It has been observed that not all large hiatus hernia patients have heartburn in their symptom profile at the time of their presentation. Therefore, the necessity of an anti-reflux procedure concurrent with the repair of the large hiatus hernia is contentious.
Methods A small prospective cohort (21) of consecutive patients diagnosed with giant hiatus hernia were evaluated for symptoms of heartburn and regurgitation at any stage during the history. A pulmonary reflux aspiration scan was additionally performed to detect reflux events objectively.
Results Heartburn or regurgitation was present in the symptomatic history of 75% (15) of patients. The pulmonary reflux aspiration scan confirmed the occurrence of reflux events in 86% (13) of patients.
Conclusion These data support the case for routine fundoplication when repairing hiatus hernia, unless otherwise contraindicated. Probably due to the configuration of para-oesophageal hiatus hernias, there is a diminution of reflux symptoms as the hernia progresses. Despite this presentation there is a high level of reflux symptomology and a high level of regurgitation shown objectively by scintigraphy, often culminating in pulmonary aspiration.

G. L. Falk, MBBS FRCS FRACS (✉) · L. Archer, FRACS MBBS (Hons) BMedSci
Concord Hospital, Hospital Road, NSW 2129 Concord, Australia
sydney.heartburn@gmail.com

L. Archer, FRACS MBBS (Hons) BMedSci
larcher@archerzone.com

G. L. Falk, MBBS FRCS FRACS · S. C. Gooley, BAdvSci (Hons)
Sydney Heartburn Clinic, Suite 29, 12 Tryon Road, NSW 2070 Lindfield, Australia
suzanna.gooley@gmail.com

Keywords Hiatus hernia · Reflux · Regurgitation · Anti-reflux surgery · Reflux aspiration

Main novel aspects

- Reflux is a common component in para-oesophageal hiatus hernias.
- Specialised reflux scintigraphy shows an objective measure of reflux, with a high (66%) frequency of reflux in cohort of patients with para-oesophageal hiatus hernias.

Introduction

There is contention in surgical circles regarding the necessity of an anti-reflux procedure concurrent with repair of large hiatus hernia. It has been observed that not all patients have heartburn in their symptom profile at the time of their presentation [1, 2]. There is a perception on the one hand, that performing fundoplication may reduce quality of life and may not be necessary (“little enders”: Gulliver’s travels [3]) and on the other, that fundoplication improves symptoms and prevents complications (“big enders”).

Excellent quality of life postoperatively has been obtained using various forms of fundoplication [4–7], though there are few studies comparing outcomes. There is one randomised controlled trial [8] in which the treatment effect is superior without a negative effect on quality of life in the fundoplication cohort.

This study evaluated a small cohort (21) of consecutive patients with giant hiatus hernia for symptomatic evidence of reflux disease at any stage during the history, and used a standardised validated pulmonary reflux aspiration scan as a minimally invasive approach to detect reflux events objectively. This was with a view to assessing the likelihood of symptomatic

benefit from fundoplication in patients undergoing repair of a large hiatus hernia.

Methods

The prospective database of the Sydney Heartburn Clinic/Concord Repatriation General Hospital was searched for consecutive patients having had the diagnosis of giant hiatus hernia over 8 months (February 2019–September 2019), evaluating symptoms of heartburn and regurgitation at any stage in the patient history (distant) and/or in the year prior to consultation, the presence of dysphagia (Fig. 1, angulation) and the results of pulmonary reflux aspiration scanning. Giant hiatus hernia, frequently synonymously known as para-oesophageal hiatus hernia (PEH), was defined as greater than 50% of the stomach in the chest and all cases were mixed hiatus hernia (type III; Fig. 1, compression).

Pulmonary reflux aspiration scanning was performed during diagnostic workup. This investigation has the potential to identify oesophageal reflux and regurgitation, pharyngeal contamination and pulmonary aspiration [9]. The investigation is performed using 40–60 MBq of 99 mTc-diethylenetriaminepentaacetic acid (DTPA) orally mixed with 150–200 ml of water. Scintigraphy images are obtained by gamma camera of the stomach, chest and upper airway for 5 min at 15 s per frame in a 64 × 64 matrix, followed by a 30-min dynamic image whilst supine for 30 s per frame. Aspiration was proven on delayed images at 2 h by the presence of isotope in the lungs. A full description of the technique has been previously published [9].

All patients gave signed informed consent to the use of data in research and the database was approved by the institutional ethics committee CH62/6/2011-092.

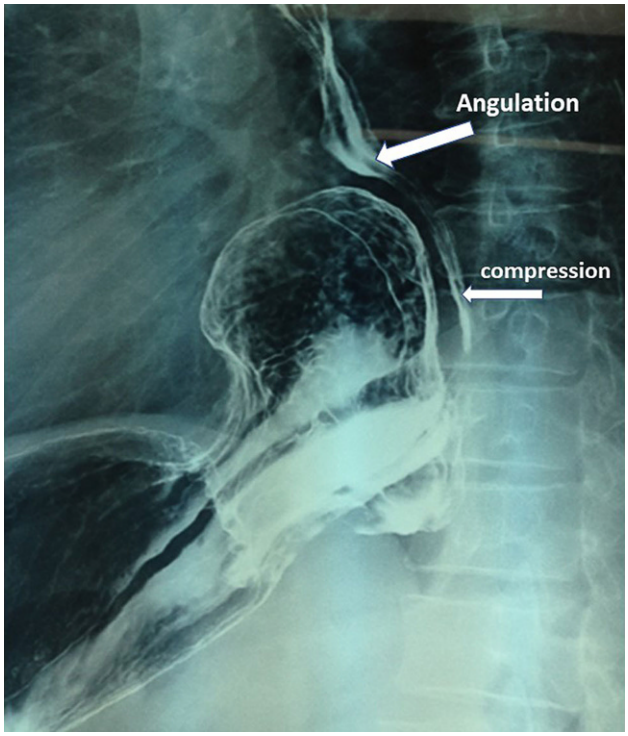


Fig. 1 Barium study showing compression of the lower oesophagus

Results

We identified 21 patients in our dataset, 20 were female. One patient was excluded due to the hernia being recurrent. The average age was 75 years, range 63–87 years. Heartburn or regurgitation was present in the distant history in 15 (75%) and recently in 13 (65%) patients. Dysphagia was current in 9 (45%) patients. Pulmonary reflux aspiration scanning had been performed in 15 patients (2 patients had clinical aspiration events and 3 patients were from distant rural sites making scintigraphy logistically challenging). Confirmed oesophageal reflux events occurred in 13 patients (86%) and pulmonary contamination was found in 10 (66%) patients.

Discussion

A startlingly high level of regurgitation and aspiration events was identified in this consecutive patient cohort. There was a concomitant high frequency of heartburn or regurgitation present in this patient group (75%). These data would support the contention that reflux/regurgitation events are relatively common in the large hiatus hernia group. This is consistent with previous studies demonstrating an association of reflux with para-oesophageal hernia (PEH) [1, 2]. Barrett's metaplasia is frequent, as shown by Le Page et al., with Barrett's oesophagus in 28% of PEH cases [4]. Similarly, Aly et al. demonstrated changes in 13% of cases on preoperative endoscopy [10]. The presence of Barrett's oesophagus indicates long-term reflux disease in a substantial proportion of patients.

It is important to note that the pulmonary aspiration events shown by testing are clinically relatively silent and of uncertain clinical effect. Data recorded did not include preceding chest infection or pneumonia, so the clinical significance of regurgitation events and scintigraphic aspiration in our group is not known. It does, however, indicate the high frequency of reflux/regurgitation events in this cohort.

Hiatus hernia has long been seen as a major contributor to the severity of reflux [11–14]. It is the nature of the formation of a PEH that there is compression of the lower oesophagus causing angulation of the cardio-oesophageal junction (anatomical derangement Fig. 1). This has a tendency to cause some level of dysphagia and functioning as an "auto fundoplication" complex, is likely to reduce the sensation of heartburn or regurgitation. This factor probably explains the oc-

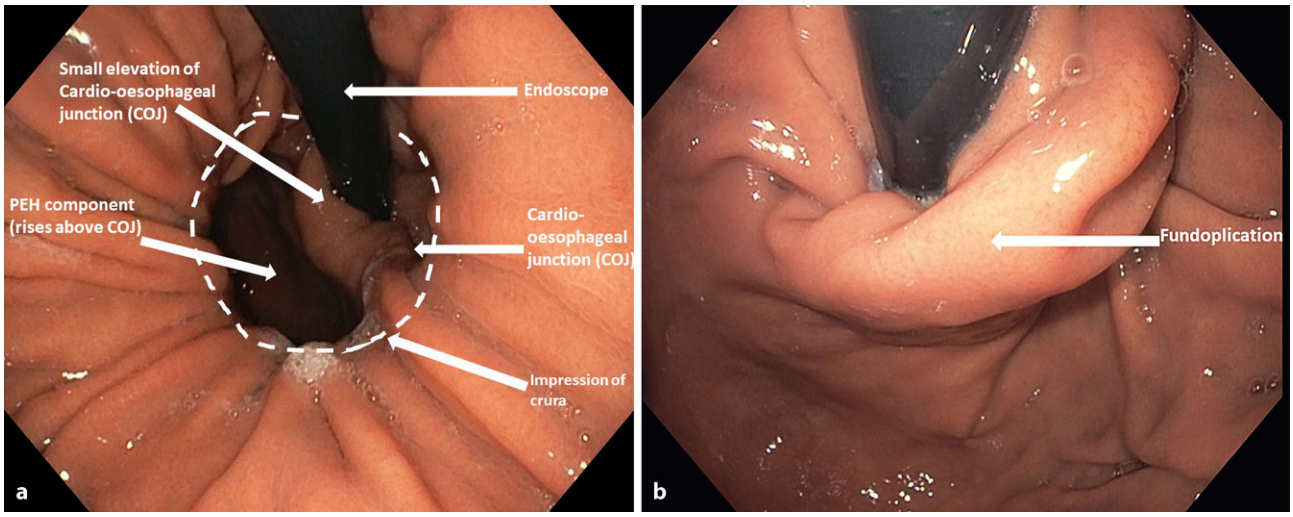


Fig. 2 Images from endoscopy, retrograde view of para-oesophageal hiatus hernia (*PEH*). **a** Endoscopic retroflexed view of PEH type III, **b** completed PEH with fundoplication (retroflexed). Images were taken using the Stryker video camera (Stryker corporation, Kalamazoo, MI, USA)

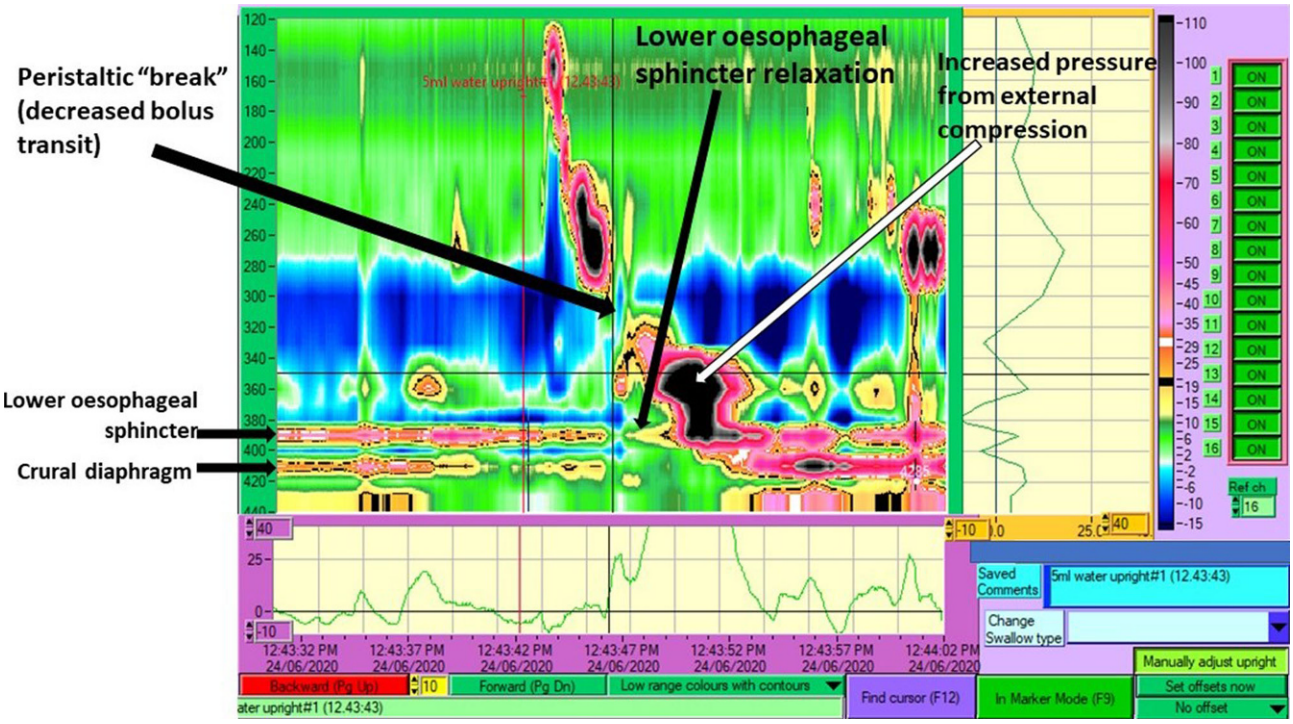


Fig. 3 High-resolution manometry with para-oesophageal hiatus hernia. Small elevation of LOS above diaphragm—type 3 (mixed hiatus hernia)

casional patient where heartburn is not necessarily a strong feature clinically or was present previously. This is not appreciated at endoscopy (Fig. 2a, b).

Retrograde movement of stomach contents into the oesophagus can take various forms, one of which is reflux disease with heartburn. Episodic regurgitation events however, associated with stasis in the intrathoracic stomach, may be heartburn negative, as the fluid within the stomach might not be particularly acidic. Impedance reflux studies demonstrate the contribution of poorly acid and non-acid regurgitation events to the spectrum of reflux disease [15, 16].

Pre-operative 24 h pH studies in PEH have not always shown elevated acid exposure times [17], confounding physicians. It is important to realise that not all regurgitation events get the characteristic pH reflux diagnostic algorithms. These events are very capable of causing significant pulmonary morbidity and mortality [18]. High-resolution manometry is frequently incomplete, as the catheter cannot be ad-

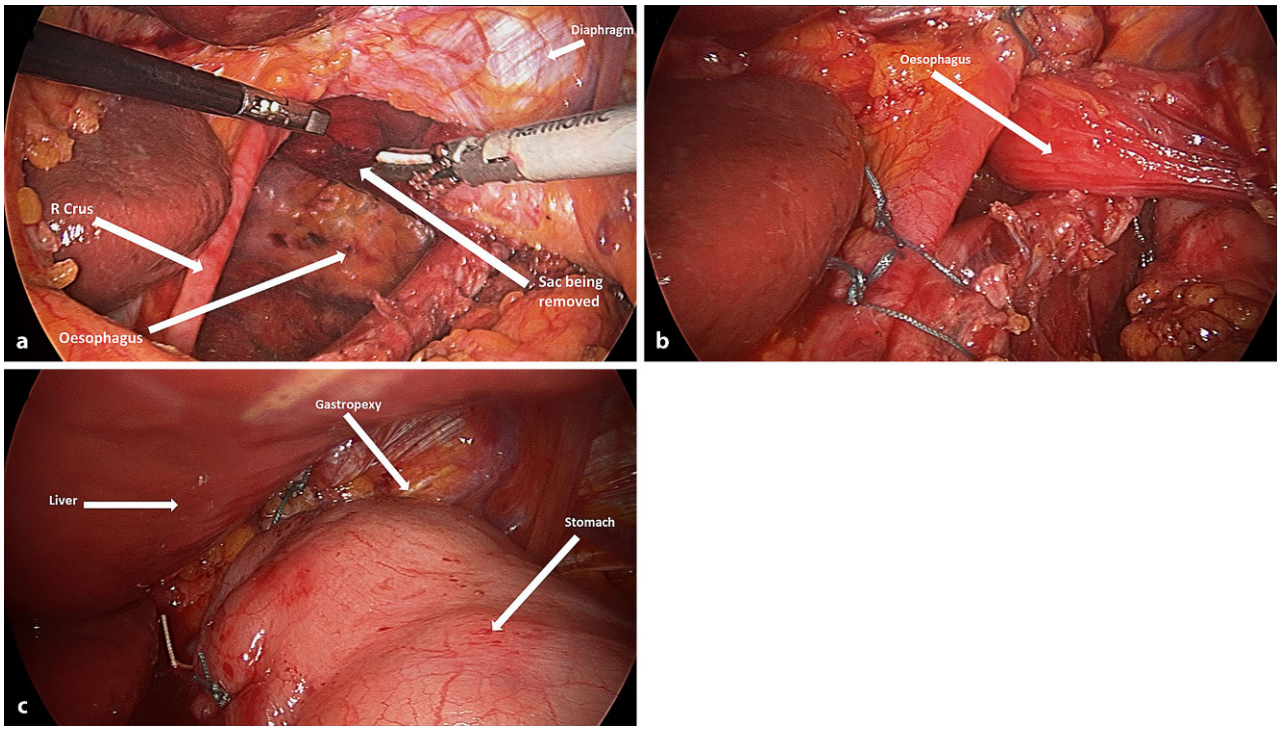


Fig. 4 Laparoscopy images of hiatal repaire showing: **a** hitus crural opening after removal of para-oesophageal hiatus hernia (PEH), hiatus defect and sac removal commenced, **b** repair of diaphragm with posterior crural approximation; **c** completed 360 fundoplication. All images were taken using the Stryker video camera (Stryker Corporation, Kalamazoo, MI, USA)

equately placed due to compression and angulation. Studies are confounded by external pressures making peristaltic assessment unpredictable or invalid (Fig. 3).

Considering the rate of heartburn clinically, the evidence for frequent pulmonary aspiration events in the patient group and signs of chronicity demonstrated by the high incidence of Barrett's oesophagus, it is very likely that large hiatus hernias are associated with reflux/regurgitation.

Repair of hiatus hernia with control of reflux disease without fundoplication is largely of historical note [19, 20]. The results of surgery until the times of Nissen [21] and Rosetti [22] were not good. Allison reported a recurrence rate of 49% in review of 421 patients with hiatus hernia repair without fundoplication [23]. Ronald Belsey also established the importance of fundoplication (Mark IV operation) through failures in trial and error with other techniques (Mark I–III) [24]. It was only with the advent of adequate forms of fundoplication that anti-reflux surgery became predictably effective.

To expect end-stage derangement of the crural mechanism to be physiologically functional with surgical manipulation of nerve supply, division of the phreno-oesophageal ligaments, which are dysfunctional in any case, and artificial repair of the deranged crural mechanism, without extra augmentation, appears fanciful. There is currently only one randomised controlled trial assessing the effectiveness of fundoplication in quality of life by Muller-Stitch et al. [8], which supports the use of fundoplication in repair of PEH (Fig. 4a, b, c).

Conclusion

The patient series reported herein demonstrates a high frequency of reflux symptoms, objective evidence for episodic regurgitation and a strikingly high incidence of pulmonary aspiration not previously demonstrated systematically. The only randomised controlled trial of fundoplication in PEH repair confirms its superiority in terms of quality of life, and these data support the case for routine fundoplication, "big enders", when repairing PEH unless otherwise contraindicated.

Compliance with ethical guidelines

Conflict of interest G.L. Falk, L. Archer and S.C. Gooley declare that they have no competing interests.

Ethical standards Institutional ethics approval CH62/6/2011-092.

References

1. Naoum C, Falk GL, Ng ACC, Lu T, Ridley L, Ing AJ, et al. Left atrial compression and the mechanism of exercise impairment in patients with a large hiatal hernia. J Am Coll Cardiol. 2011;58(15):1624–34.

2. Carroll TL, Nahikian K, Asban A, Wiener D. Nissen fundoplication for laryngopharyngeal reflux after patient selection using dual pH, full column impedance testing: a pilot study. Ann Otol Rhinol Laryngol. 2016;125(9):722–8.
3. Swift J. Travels into several remote nations of the world. Glasgow: James Knox; 1765.
4. Le Page PA, Furtado R, Hayward M, Law S, Tan A, Vivian SJ, et al. Durability of giant hiatus hernia repair in 455 patients over 20 years. Ann R Coll Surg Engl. 2015;97(3):188–93.
5. Shukri MJ, Watson DI, Lally CJ, Devitt PG, Jamieson GG. Laparoscopic anterior 90° fundoplication for reflux or large hiatus hernia. ANZ J Surg. 2008;78(3):123–7.
6. el-Sherif AE, Adusumilli PS, Pettiford BL, d'Amato TA, Schuchert MJ, Clark A, et al. Laparoscopic clam shell partial fundoplication achieves effective reflux control with reduced postoperative dysphagia and gas bloating. Ann Thorac Surg. 2007;84(5):1704–9.
7. Cai W, Watson DI, Lally CJ, Devitt PG, Game PA, Jamieson GG. Ten-year clinical outcome of a prospective randomized clinical trial of laparoscopic Nissen versus anterior 180° partial fundoplication. Br J Surg. 2008;95(12):1501–5.
8. Müller-Stich BP, Linke GR, Senft J, Achtstätter V, Müller PC, Diener MK, et al. Laparoscopic mesh-augmented hiatoplasty with cardiophrenicopexy versus laparoscopic Nissen fundoplication for the treatment of gastroesophageal reflux disease: a double-center randomized controlled trial. Ann Surg. 2015;262(5):721–7.
9. Falk M, Van der Wall H, Falk GL. Differences between scintigraphic reflux studies in gastrointestinal reflux disease and laryngopharyngeal reflux disease and correlation with symptoms. Nucl Med Commun. 2015;36(6):625–30.
10. Aly A, Munt J, Jamieson GG, Ludemann R, Devitt PG, Watson DI. Laparoscopic repair of large hiatal hernias. Br J Surg. 2005;92(5):648–53.
11. Kahrilas PJ. The role of hiatus hernia in GERD. Yale J Biol Med. 1999;72(2/3):101–11.
12. Roman S, Kahrilas PJ. The diagnosis and management of hiatus hernia. BMJ. 2014;349:g6154.
13. Kahrilas PJ, Shi G, Manka M, Joehl RJ. Increased frequency of transient lower esophageal sphincter relaxation induced by gastric distention in reflux patients with hiatal hernia. Gastroenterology. 2000;118(4):688–95.
14. Wright RA, Hurwitz AL. Relationship of hiatal hernia to endoscopically proved reflux esophagitis. Dig Dis Sci. 1979;24(4):311–3.
15. Zerbib F, Bruley Des Varannes S, Roman S, Pouderoux P, Artigue F, Chaput U, et al. Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian—French cohort of healthy subjects. Aliment Pharmacol Ther. 2005;22(10):1011–21.
16. Park W, Vaezi MF. Esophageal impedance recording: clinical utility and limitations. Curr Gastroenterol Rep. 2005;7(3):182–9.
17. Fuller C, Hagen J, Demeester T, Peters J, Ritter M, Bremmer C. The role of fundoplication in the treatment of type II paraesophageal hernia. J Thorac Cardiovasc Surg. 1996;111:655–61.
18. Rantanen TK, Salo JA. Gastroesophageal reflux disease as a cause of death: analysis of fatal cases under conservative treatment. Scand J Gastroenterol. 1999;34(3):229–33.
19. Allison PR. Reflux esophagitis, sliding hiatal hernia, and the anatomy of repair. Surg Gynecol Obstet. 1951;92(4):419–31.
20. Stylopoulos N, Rattner DW. The history of hiatal hernia surgery: from Bowditch to laparoscopy. Ann Surg. 2005;241(1):185–93.
21. Nissen R. A simple operation for control of reflux esophagitis. Schweiz Med Wochenschr. 1956;86(Suppl 20):590–2.
22. Rossetti M, Hell K. Fundoplication for the treatment of gastroesophageal reflux in hiatal hernia. World J Surg. 1977;1(4):439–43.
23. Allison PR. Hiatus hernia: (a 20-year retrospective survey). Ann Surg. 1973;178(3):273–6.
24. Orringer MB, Skinner DB, Belsey RHR. Long-term results of the Mark IV operation for hiatal hernia and analyses of recurrences and their treatment. J Thorac Cardiovasc Surg. 1972;63(1):25–33.

review

Eur Surg (2019) 51:291–294
https://doi.org/10.1007/s10353-019-00612-4

european surgery
ACA Acta Chirurgica Austriaca

Giant hiatus hernia: closure of the difficult hiatus

Gregory L. Falk · Trevor J. D'Netto · Sophia C. Little

Received: 8 August 2019 / Accepted: 22 August 2019 / Published online: 27 September 2019

Summary
Background Repair of the large hiatus hernia has been troubled by diaphragmatic hiatal repair failure and recurrence. Use of mesh repair may reduce recurrence at a cost of increased reoperative complications and mesh fistulation. Methods of hiatal closure facilitation are described.
Methods Techniques and accompanying intra-surgery pictures are discussed here based on personal experience from within a service performing variable 100 giant hernia repairs annually.
Results Techniques for closure of a large hiatus without mesh repair are described with illustration, the purpose to expose various techniques utilized in a service performing more than 100 giant hernia repairs annually.
Conclusion Techniques adopted and described in this article may facilitate both mesh and non-mesh repair of crural hiatal defects associated with giant hiatus hernia.

Keywords Giant Hiatus Hernia · Para-oesophageal · Recurrence · Hiatus repair · Technique

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10353-019-00612-4) contains supplementary material, which is available to authorized users.

G. L. Falk, MB.BS, FRACS, FACS (✉) · S. C. Little, B. AVBS (Hons I)
Sydney Heartburn Clinic, Suite 29, 12 Tryon Road, 2070 Lindfield, NSW, Australia
sydney.heartburn@gmail.com

S. C. Little, B. AVBS (Hons I)
sophia.little7@gmail.com

G. L. Falk, MB.BS, FRACS, FACS
Cl/A Professor of Surgery, University of Sydney, Sydney, NSW, Australia

Concord Repatriation Hospital, Concord, NSW, Australia

T. J. D'Netto, MBBS (Hons)
Sydney Adventist Hospital, Wahroonga, NSW, Australia
dnetto@optusnet.com.au

Background

Repair of giant hiatus hernia has been troubled by diagrammatic hiatus repair failure and recurrence [1–3]. This has led to the development of multiple techniques in an effort to reduce recurrence rates. The use of added mesh repair is frequent [4]. Because of the recognized problems of erosion and resection and poor outcome with reoperative surgery in mesh implants, it has been our preferred option to perform repair of the diaphragmatic hiatus by a suture alone. Disappointing experiences using Teflon pledget-buttressed fundoplication highlighted the problems associated with foreign material around the hiatus [5, 6]. Several publications have highlighted reoperative difficulties with mesh, the largest being that of Stadlhuber and colleagues [7].

Method

Techniques have been developed by the author for non-mesh closure of large hiatal defects. This may be useful to other practitioners confronting similar problems. Personal experience is discussed.

All pictures were obtained during surgery using digital USB downloads from Stryker laparoscopic camera.

Results

Techniques utilized in our service over many years are described in this brief report with pictures to facilitate use by others.

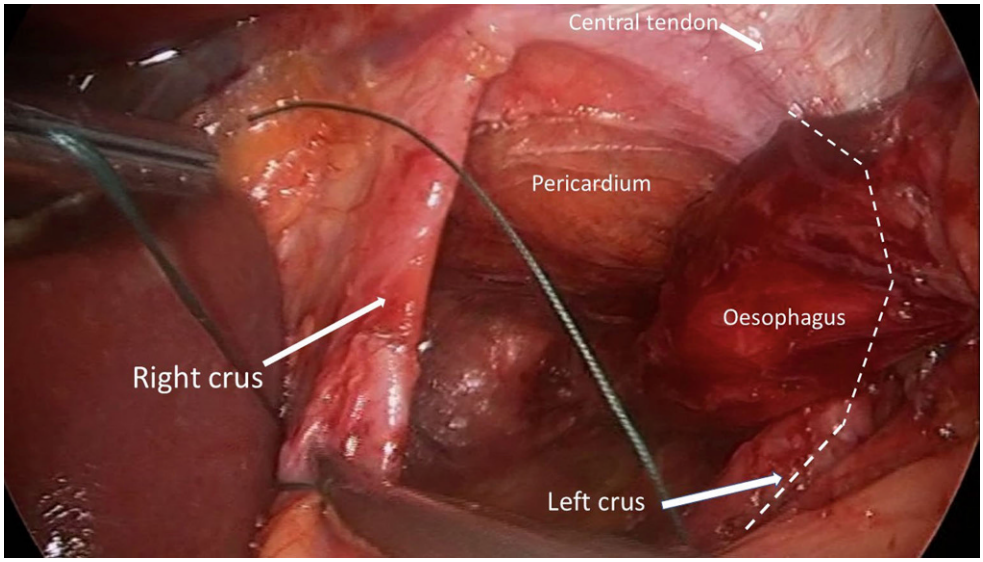


Fig. 1 Intra-surgery image of pericardium due to anterior central tendon diaphragm defect. Image was taken using Stryker video camera

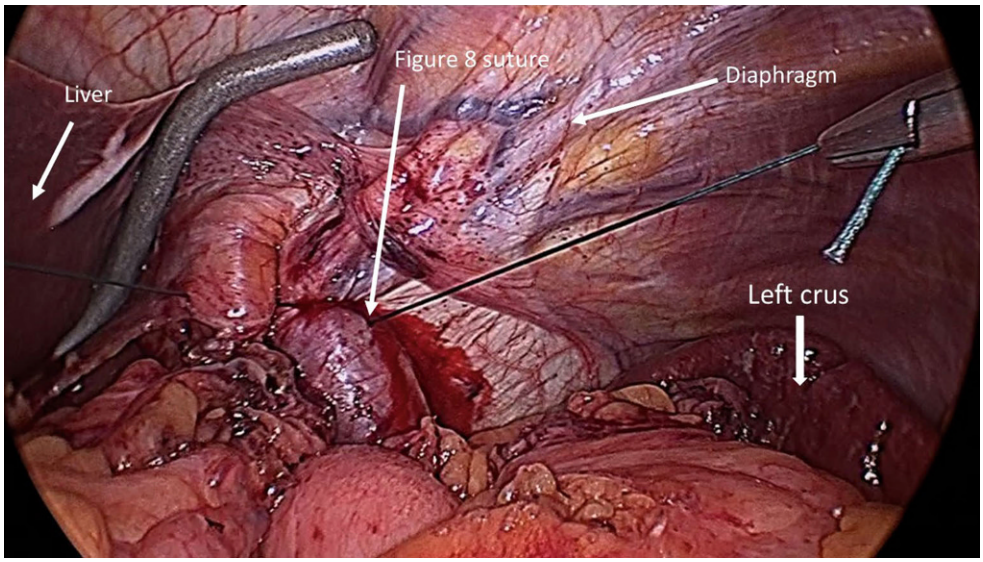


Fig. 2 Intra-surgery image of anterior suture large diaphragmatic defect. Image was taken using Stryker video camera

Retraction of the hiatus During exposure and retraction of the liver in the laparoscopic repair of giant hiatus hernia, the pillars of the crus are tensioned by the anterior and caudal placement of the retractor (Fig. 1). Once dissection is complete and esophageal and gastric mobility ensured, the retractor may be detensioned to allow for greater movement of the hiatal pillars and less tension in the approximation of the crura.

Intra-abdominal pressure The intraperitoneal gas at laparoscopy distracts the tissues and tensions the diaphragm. Reduction in pressure following full dissection reduces tension in the diaphragm and the diaphragmatic crura and may be altered dependent upon exposure for suturing.

Anterior plication of the crura In large hiatus hernia there is frequently distraction of the anterior crural mechanism well into the central tendon. This is obvious upon dissection where the pericardium is well in view unlike in smaller hiatus hernia (Fig. 2). Closure of the defect in the central tendon relieves pressure on the posterior repair and is quite advantageous. Sutures are placed to avoid pericardium but are through dense fibrous tissue. The figure-of-eight technique is especially technically helpful.

Left diaphragm recruitment It is noticeable that the left crural pillar moves across to fill the diaphragmatic gap during repair of the hiatus. The movement of the left diaphragm is obliquely anterio-medial and not transverse. This understanding is important for suture placement. Dissection of the sulcus posterior to the gastro-phrenic ligament facilitates the anterior movement of the left diaphragm (Fig. 3 and supplementary video). Movement of the left hemi diaphragm is well demonstrated in the supplementary video. Su-

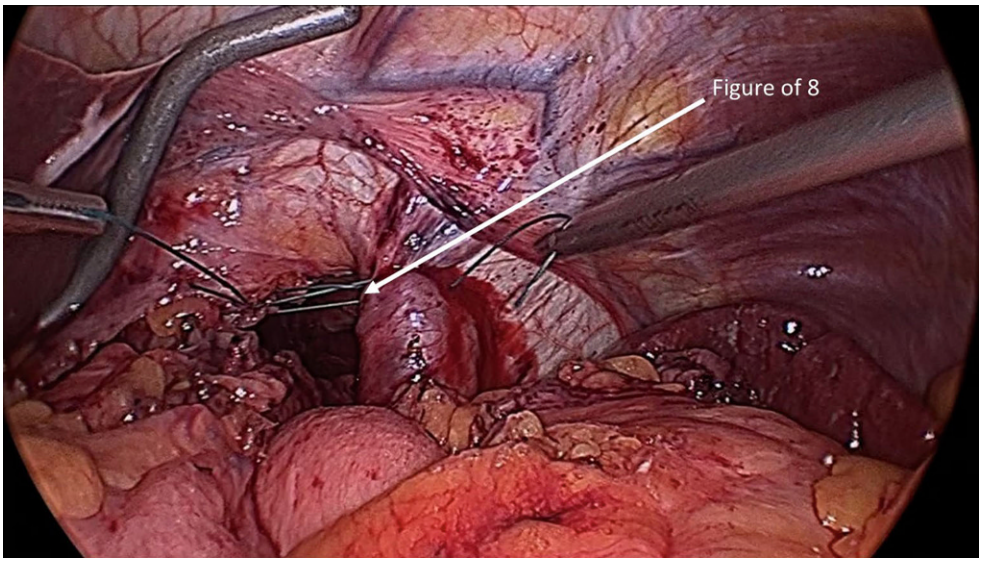


Fig. 3 Image of sutures placed in anterior repair during surgery. Image was taken using Stryker video camera

tures are necessarily placed to approximate the pillars obliquely.

Suture The use of a figure-of-eight suture is very advantageous in allowing the apposition of tissues. Less tension and less tissue ischemia are apparent by comparison with multiple single sutures. Closure of the anterior defect first may reduce tension in the posterior repair in some patients with very large hiatus defects.

Pneumothorax The use of pneumothorax in the left chest as an aid to hiatus closure has been described [8]. We have found accidental pneumothorax (capnothorax [9]) can lead to sudden cardiopulmonary decompensation and hypotension best avoided. One would recommend judicious and facile performance of such a technique at lower installation pressure of the peritoneal CO_2 cognizant of its potential risk. There is little doubt, however, that pneumothorax allows flattening of the left diaphragm and easier approximation of the crural pillars.

Releasing incision Release has been performed in the authors' series of 785 patients having surgery for giant hiatus hernia a total of three times to allow for hiatus repair. On each occasion it has been a calculated incision posterior in the left lateral diaphragm, performed vertically and transversely closed with O-Ethibond, usually situated behind the upper splenic pole. It is also associated with pneumothorax. The site of diaphragmatic incision was chosen to possibly lessen the risk of bowel hernia through a potential diaphragmatic weakness. Right crural releasing incision has been recommended [10], but is potentially fraught owing to the poor tissues for placement of mesh fixation and the minimal area of tissue for adherence of the mesh. Additionally, such an incision will separate the muscle from the fibrous tissue in the crural pillar potentially weakening the whole apparatus. Reports of this technique are currently quite short-term and in a small number of cases.

Recurrence rates of hernia in this difficult patient group utilizing these techniques have been reported. The recurrence rate of any size was 35.6% at a median of 42 months [1], with more than half of patients being asymptomatic. In this cohort there was a reoperation rate of 4.8%. Another cohort at 2 years showed a 9% recurrence with only 2% of symptomatic patients [11]. We have more recently reported improved recurrence rates in the shorter term using a more complex technique of cardiopexy fixation with similar hiatus repair [12]. These techniques have obviated the need for mesh augmented repair and have facilitated diaphragmatic repair.

Discussion

A variety of surgical techniques have been utilized in the prevention of recurrent giant hiatus hernia and have similar recurrence rates [13–18].

These include mesh in a variety of positions, biological or synthetic, esophageal lengthening and, in some, diaphragmatic releasing incision resulting in similar recurrence rates.

Because of experiences of mesh-related reoperative complications (unpublished data, [7, 18]) we have included repair without mesh. Herein is a description of techniques utilized that have been effective and offer reasonable recurrence rates [1, 19].

Conclusion

Techniques adopted and described in this article may facilitate both mesh and non-mesh repair of crural hiatal defects associated with giant hiatus hernia.

Compliance with ethical guidelines

Conflict of interest G.L. Falk, T.J. D'Netto, and S.C. Little declare that they have no competing interests.

Ethical standards Prospective patient data were collated from a password-protected practice database and collated for publication. The database was approved by the institutional ethics (CH62/6/2011-092).

References

1. Le Page PA, Furtado R, Hayward M, Law S, Tan A, Vivian SJ, et al. Durability of giant hiatus hernia repair in 455 patients over 20 years. Ann R Coll Surg Engl. 2015;97(3):188–93.
2. Luketich JD, Nason KS, Christie NA, Pennathur A, Jobe BA, Landreneau RJ, et al. Outcomes after a decade of laparoscopic giant paraesophageal hernia repair. J Thorac Cardiovasc Surg. 2010;139(2):395–404.e1.
3. Dallemagne B, Weerts J, Markiewicz S, Dewandre J-M, Wahlen C, Monami B, et al. Clinical results of laparoscopic fundoplication at ten years after surgery. Surg Endosc Other Interv Tech. 2006;20(1):159–65.
4. Müller-Stich BP, Kenngott HG, Gondan M, Stock C, Linke GR, Fritz F, et al. Use of mesh in laparoscopic paraesophageal hernia repair: a meta-analysis and risk-benefit analysis. PLoS ONE. 2015;10(10):e139547.
5. Baladas HG, Smith GS, Richardson MA, Dempsey MB, Falk GL. Esophagogastric fistula secondary to teflon pledget: a rare complication following laparoscopic fundoplication. Dis Esophagus. 2000;13(1):72–4.
6. Dally E, Falk GL. Teflon pledget reinforced fundoplication causes symptomatic gastric and esophageal lumenal penetration. Am J Surg. 2004;187(2):226–9.
7. Stadlhuber RJ, Sherif AE, Mittal SK, Fitzgibbons RJ, Michael Brunt L, Hunter JG, et al. Mesh complications after prosthetic reinforcement of hiatal closure: a 28-case series. Surg Endosc. 2009;23(6):1219–26.
8. Low DE, Simchuk EJ. Effect of paraesophageal hernia repair on pulmonary function. Ann Thorac Surg. 2002;74(2):333–7.
9. Phillips S, Falk GL. Surgical tension pneumothorax during laparoscopic repair of massive hiatus hernia: a different situation requiring different management. Anaesth Intensive Care. 2011;39(6):1120.
10. Alicuben ET, Worrell SG, DeMeester SR. Impact of crural relaxing incisions, Collis gastroplasty, and non-cross-linked human dermal mesh crural reinforcement on early hiatal hernia recurrence rates. J Am Coll Surg. 2014;219(5):988–92.
11. Gibson SC, Wong SC, Dixon AC, Falk GL. Laparoscopic repair of giant hiatus hernia: prosthesis is not required for successful outcome. Surg Endosc. 2013;27(2):618–23.
12. Furtado RV, Vivian SJ, van der Wall H, Falk GL. Medium-term durability of giant hiatus hernia repair without mesh. Ann R Coll Surg Engl. 2016;98(7):450–5.
13. Rathore MA, Andrabi SIH, Bhatti MI, Najfi SMH, McMurray A. Metaanalysis of recurrence after laparoscopic repair of paraesophageal hernia. JSLS. 2007;11(4):456–60.
14. Mehta S, Boddy A, Rhodes M. Review of outcome after laparoscopic paraesophageal hiatal hernia repair. Surg Laparosc Endosc Percutaneous Tech. 2006;16(5):301–6.
15. Nason KS, Luketich JD, Qureshi I, Keeley S, Trainor S, Awais O, et al. Laparoscopic repair of giant paraesophageal hernia results in long-term patient satisfaction and a durable repair. J Gastrointest Surg. 2008;12(12):2066–77.
16. Dallemagne B, Kohnen L, Perretta S, Weerts J, Markiewicz S, Jehaes C. Laparoscopic repair of paraesophageal hernia: long-term follow-up reveals good clinical outcome despite high radiological recurrence rate. Ann Surg. 2011;253(2):291–6.
17. Hashemi M, Peters JH, DeMeester TR, Huprich JE, Quek M, Hagen JA, et al. Laparoscopic repair of large type III hiatal hernia: objective followup reveals high recurrence rate⟨sup⟩1⟨/sup. J Am Coll Surg. 2000;190(5):553–60.
18. Oelschlager BK, Pellegrini CA, Hunter JG, Brunt ML, Soper NJ, Sheppard BC, et al. Biologic prosthesis to prevent recurrence after laparoscopic paraesophageal hernia repair: long-term follow-up from a multicenter, prospective, randomized trial. J Am Coll Surg. 2011;213(4):461–8.
19. Gibson SC, Wong SK, Dixon AC, Falk GL. Laparoscopic repair of giant hiatus hernia: prosthesis is not required for successful outcome. Surg Endosc. 2013;27(2):618–23.

Royal College of Surgeons
ADVANCING SURGICAL CARE

UPPER GI SURGERY

Ann R Coll Surg Engl 2016; **98:** 450–455
doi 10.1308/rcsann.2016.0156

Medium-term durability of giant hiatus hernia repair without mesh

RV Furtado[1], SJ Vivian[2], H van der Wall[3], GL Falk[1,2]

[1]Concord Repatriation General Hospital, NSW, Australia
[2]Sydney Heartburn Clinic, Lindfield, NSW, Australia
[3]Concord Nuclear Imaging, NSW, Australia

ABSTRACT

INTRODUCTION This is the second report on objective review of 100 patients who underwent composite fundoplication-cardiopexy for repair of giant hiatus hernia (GHH) at a median of 24 months following surgery. Outcomes were objective follow-up by endoscopy and quality of life (QoL) by Gastrointestinal Quality of Life Index (GIQLI), modified Visick scores and dysphagia scores. The initial report for this cohort suggested a low objective recurrence rate (9%) and substantial improvements in QoL indices.

METHODS The rate of hernia recurrence was assessed with Kaplan–Meier analysis and covariates were analysed with the Cox proportional hazards model. Paired t-tests and related samples Wilcoxon signed-rank tests were used to compare QoL scores. Unpaired data were compared with the independent samples t-test and Mann–Whitney U test.

RESULTS Objective review was obtained in 97% of the patients. There were five recurrences of hernias that had a vertical height of >2cm from the diaphragmatic hiatus, with three patients requiring reoperation for severe dysphagia. Small recurrences (<2cm) occurred in 20 patients. The median time to recurrence was 40 months (95% confidence interval: 34–46 months). At two years, recurrence of any size had occurred in 24% of cases. At follow-up review (median: 27 months), the mean GIQLI score was 109 (p=0.279), the median modified Visick score was 2 (p=0.954) and the median dysphagia score was 41 (p=0.623). There was no evidence that the GIQLI score (p=0.089), the modified Visick score (p=0.339) or the dysphagia score (p=0.445) changed significantly after recurrence.

CONCLUSIONS There was a sustained improvement in overall QoL and reflux scores after GHH repair. QoL scores showed persistent improvement in reflux and overall health, even in the subgroup with recurrence. The majority (80%) of recurrences were small and recurrent herniation did not appear to significantly change QoL. The rates of recurrence and QoL are comparable with those for other methods of repair.

KEYWORDS
Paraoesophageal hiatus hernia – Laparoscopy – Follow-up study – Quality of life

Accepted 28 June 2015

CORRESPONDENCE TO
Ruelan Furtado, E: ruelanfurtado@yahoo.co.uk

Giant hiatus hernia (GHH) increasingly presents for surgical repair.[1] Management of the short oesophagus,[2] a wide hiatus[3] and severe reflux[4] remains controversial, however. Furthermore, the question of durability remains unanswered and uncertainty exists as to the best form of operative procedure, including mesh repair of the hiatus.

Composite fundoplication has been performed by the senior author (GLF) since 2009, in an attempt to improve recurrence. The principles of the operation include extensive mediastinal dissection to mobilise the oesophagus, repair of the hiatus with deep sutures through the fascial component of the crural pillars, a 360° fundoplication and posterior cardiopexy.[5]

Early outcome (at a mean of 574 days following surgery) of the first 100 consecutive cases was published in 2013.[6] In that study, objective follow-up review was achieved in 97% of patients at four months. Early recurrence was observed in nine cases (2 large, 7 small hernias) and reoperation in two. QoL scores were significantly improved after surgery (p<0.0001). The modified Visick score[7] fell from a median of 3.0 to 1.7. The mean Gastrointestinal Quality of Life Index (GIQLI)[8] improved from 87.8 (standard deviation [SD]: 24) preoperatively to 109.1 (SD: 22). There was evidence (p=0.03) that the mean GIQLI score in patients with recurrence (94, SD: 24.6) was worse than in those without recurrence (110, SD: 21.8).

This paper describes the same cohort now at a mean of 1,207 days (SD: 260 days) following surgery. Outcome measures were QoL, hernia recurrence, reoperation and postoperative oesophagitis.

Methods

A prospective database of the first 100 patients undergoing composite repair has been maintained on Access® (Microsoft, Redmond, WA, US). The cohort was verified and 4 patients in the 100 reported previously[6] violated protocol: There was one duplication and overestimation of hernia size in three patients. These patients were replaced by the next sequential patients in the cohort. Consent to further follow-up review was withdrawn by five patients (2 psychogeriatric diagnoses, 2 with frailty, 1 refusal for further tests) but reporting of existing results was permitted.

Age, sex, body mass index (BMI) and ASA (American Society of Anesthesiologists) grade were recorded. The size of the hernia was estimated during the operation, according to established criteria. Operative variables were the number of sutures in the hiatal repair and whether there was perceived tension on the hiatus during closure. Tension was assessed by the senior author (GLF), based on substantial operative experience, as pressure required to gain apposition of the crural pillars. Details were recorded in a standardised proforma and transferred to the database.

Hernia size was estimated by a combination of radiological and intraoperative assessment, and was expressed by the percentage of stomach in the mediastinum. The landmarks used at laparoscopy were the pylorus (100% herniation), crow's foot (75%) and a point halfway between the crow's foot and angle of His (50%). The size of the hiatus was classified by surgical estimation as moderately large, large or very large.

Review process

Mail review and phone interviews were used to assess QoL by GIQLI, the modified Visick score and the Dakkak score for dysphagia.[9] GIQLI comprises a 144-point scale based on 36 questions. The modified Visick scale has four categories: grade 1 (no symptoms), grade 2 (minimal symptoms, no lifestyle changes), grade 3 (significant symptoms requiring lifestyle changes and medical consultation) and grade 4 (severe or recurrent symptoms interfering with enjoyment of life). The Dakkak dysphagia score has a range of 0 (severe dysphagia) to 45 (normal swallowing), based on nine questions. While GIQLI and the modified Visick score were shown to improve significantly after surgery in the initial report, no comparison was made of dysphagia scores.[6]

Early (within 12 months) and later (after 12 months) postoperative QoL scores were compared to establish the durability of symptom improvement. Paired and unpaired comparisons were made of the initial GIQLI, modified Visick and dysphagia scores from the first year after surgery with the most recent scores. Scores at later postoperative follow-up review were also compared with preoperative scores.

Paired analysis of QoL was also carried out in the recurrence subgroup. Two comparisons were made. First, GIQLI, modified Visick and dysphagia scores were compared prior to and after surgery but before recurrence was noted. Second, postoperative scores were compared before and after recurrence.

Anatomical follow-up review was predominantly with endoscopy. This took place at least once in the first year after surgery and was then planned every 2–3 years thereafter. The presence of a recurrent hernia, oesophagitis (on endoscopy), Barrett's oesophagus (on endoscopy and histology) and gastric residue was noted. Where endoscopy was impractical, patients undertook a barium meal and the radiographs were obtained for review.

Recurrence was categorised as a hernia of either <2cm or >2cm of intrathoracic stomach, measured vertically from the hiatus. Three types of recurrence were noted (Fig 1). Telescoping recurrence occurred when the gastro-oesophageal junction (GOJ) slipped through the fundoplication, which remained below the diaphragm itself. Hiatal failure arose when the GOJ and fundoplication herniated through the hiatus. Finally, paraoesophageal recurrence was identified when there was herniation of the stomach into the mediastinum, with the GOJ remaining in the abdomen.[10]

Statistical analysis

SPSS® version 21 (IBM, New York, US) was used for analysis. Nonparametric data were analysed with the related samples Wilcoxon signed-rank test. Parametric data were analysed with the paired t-test. Unpaired data were compared with the independent samples t-test and Mann–Whitney U test. Time to recurrence and median follow-up were analysed using Kaplan–Meier and reverse Kaplan–Meier methods.[11] Covariates were analysed with the Cox proportional hazards model. Multivariate regression was carried out if the p-value was ≤0.1 on univariate regression. Statistical significance was accepted at $p<0.05$.

Results

The mean patient age at the most recent review was 71 years (SD: 10.2 years) and 71 patients were female. Other patient variables are described in the initial report[6] and in Table 1. One postoperative mortality was described in the initial report. Since then, a further patient died of causes unrelated to surgery.

Hernia recurrence

Ninety-seven patients (97%) underwent anatomical review at a median of 24 months (95% confidence interval [CI]: 20–28 months) following surgery. A recurrent hernia was found in 24 patients (24%). Five (5%) were larger than 2cm. Hiatal failure occurred in 13, telescoping recurrence in 9 and paraoesophageal recurrence in 2 patients (Table 2). The median time to recurrence was 40 months (95% CI: 34–46 months).

QoL: early postoperative vs later postoperative scores

Early follow-up scores were recorded at a median of 2 months (range: 1.0–11.9 months) and later review was at a median of 27 months (range: 12.0–51.6 months). There was an 85% response rate to QoL follow-up.

Paired QoL data for GIQLI were available in 70 patients. The mean GIQLI score was 107 (SD: 20.3) at early follow-up review and 109 (SD: 21.3) at later review. There was no evidence of a significant change between periods (mean

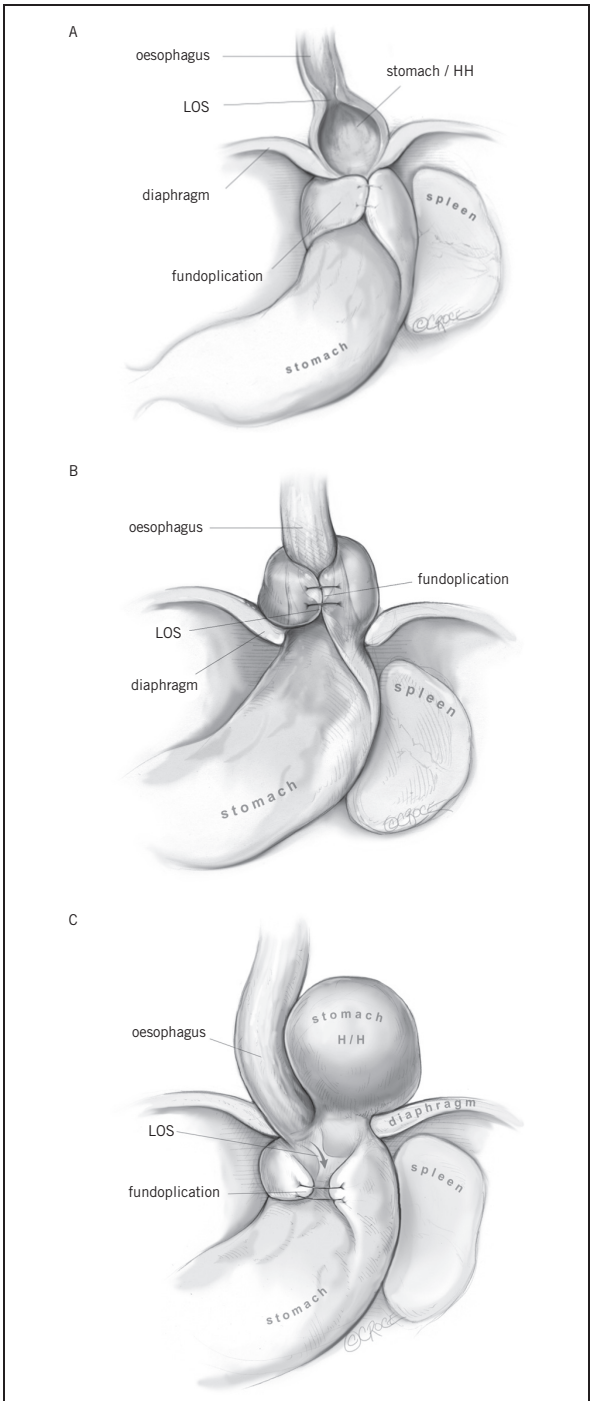


Figure 1 Telescoping recurrence (A), hiatal failure (B) and paraoesophageal recurrence (C)

Table 1 Patient characteristics

Characteristic	Number	Missing data
Mean age at follow-up (years)	72.0 (SD: 10.2)	0%
Patients with tension on completed hiatal repair	6	14%
Size of hiatus: moderate / large / very large	11 / 69 / 14	6%
Mean number of hiatal sutures	3.8 (SD: 0.82)	6%
Body mass index (kg/m^2)	29 (range: 20–44)	30%
ASA grade: 1 / 2 / 3 / 4	4 / 38 / 27 / 2	29%
Size of hernia (% in mediastinum)	75% (range: 20–100%)	6%

SD = standard deviation; ASA = American Society of Anesthesiologists

Table 2 Size and type of recurrent hiatal hernias

Type of recurrence	Recurrence <2cm	Recurrence >2cm	Total
Hiatal failure	9	4	**13**
Telescoping	8	1	**9**
Paraoesophageal	2	0	**2**
Total	**19**	**5**	**24**

difference: -2.4, 95% CI: -6.7–2.0, t=-1.09, df=69, p=0.279). Paired Visick scores were available in 66 patients. The median modified Visick score was 2 (range: 1–4) at both early and later follow-up review (p=0.954). Paired dysphagia scores were available in 65 patients. The median dysphagia score at early follow-up review was 41 (range: 8–45) and at later review, it was also 41 (range: 10–45). This was not significantly different (p=0.623). Unpaired data analysis yielded similar results (Tables 3 and 4).

QoL: preoperative vs later postoperative scores

The mean preoperative GIQLI score was 89 (SD: 24.6) (n=90), improving to 108 (SD: 21.6) (n=84) at later postoperative review (p<0.001). The median preoperative modified Visick score was 3 (range: 1–4) (n=84) and improved to 2 (range: 1–4) (n=82) at later postoperative review (p<0.001). The median preoperative dysphagia score was 35 (range: 1–45) (n=85) while the median later postoperative score was 30 (range: 10–45) (n=81) (p=0.072).

QoL after hernia recurrence

Table 5 shows paired analyses of QoL scores for the 24 patients who developed recurrent hernias. GIQLI (paired data available for 18 patients) improved significantly after

Table 3 Quality of life scores (paired analysis)

Indicator	Early postoperative	Later postoperative	*p*-value
Mean GIQLI (*n*=70)	107 (SD: 20.3)	109 (SD: 21.3)	0.279*
Median Visick score (*n*=66)	2 (1–4)	2 (1–4)	0.954**
Median dysphagia score (*n*=65)	41 (8–45)	40.5 (10–45)	0.623**

GIQLI = Gastrointestinal Quality of Life Index; SD = standard deviation
*paired t-test; **related samples Wilcoxon signed-rank test

surgery from a mean score of 92 to 108 (p=0.004). After recurrence, the mean GIQLI score remained 106. This was not significantly different from the mean GIQLI score prior to recurrence (p=0.089). The modified Visick score (paired data available for 15 patients) improved from a median of 4 preoperatively to 2 after surgery (p=0.001). After recurrence, it remained at a median of 2 (p=0.339). The median dysphagia score (paired data available for 16 patients) prior to surgery was 33. There was no evidence to suggest this changed after surgery (median: 37, p=0.507) or after recurrence (median: 45, p=0.445).

Using Cox multivariate regression analysis, recurrence was found to be significantly more likely in patients older than 70 years at surgery (hazards ratio [HR]: 3.0, 95% CI: 1.2–7.4, p=0.017) and also where the surgeon noted there was tension on the completed hiatal repair (HR: 4.1, 95% CI: 1.1–14.7, p=0.032) (Table 6). Tension on hiatal repair was considered present in six patients and three (50%) developed recurrences. Recurrence occurred in 16 (34%) of the 47 patients over the age of 70 years.

Oesophagitis, Barrett's oesophagus and delayed gastric emptying

Oesophagitis occurred in five patients (5%) following surgery, two having a recurrent hernia at the time of diagnosis. Barrett's oesophagus was noted in 27 patients (27%). Gastric residue was found in 19 cases (19%) on endoscopy despite an overnight fast.

Discussion

Low morbidity and reoperation rates and sustained improvement to QoL are predictable outcomes following GHH repair. Overall QoL and reflux outcomes were sustained at two years. The hernia recurrence rate (24%) was comparable with those in other series with routine objective follow-up.[12,13] Reoperation (3%) was less frequent than in these studies.

Table 4 Quality of life scores (unpaired analysis)

Indicator	Preoperative	Early postoperative	Later postoperative	*p*-value, preoperative vs early postoperative	*p*-value, early vs later postoperative	*p*-value, preoperative vs later postoperative
Mean GIQLI	89 (SD: 24.6) *n*=90	106 (SD: 20.3) *n*=84	108 (SD: 21.6) *n*=84	**<0.001**	0.557	**<0.001**
Median Visick score	3 (range: 1–4) *n*=84	2 (range: 1–4) *n*=81	2 (range: 1–4) *n*=82	**<0.001**	0.586	**<0.001**
Median dysphagia score	35 (range: 1–45) *n*=85	41 (range: 4–45) *n*=80	39 (range: 10–45) *n*=81	0.051	0.836	0.065

GIQLI = Gastrointestinal Quality of Life Index; SD = standard deviation

Table 5 Quality of life scores after recurrence in 24 patients (paired analysis)

Indicator	Preoperative	Postoperative, before recurrence	Postoperative, after recurrence	*p*-value, preoperative vs after recurrence	*p*-value, before recurrence vs after recurrence
Mean GIQLI (*n*=18)	92 (SD: 21)	108 (SD: 11)	106 (SD: 20)	**0.004***	0.089*
Median Visick score (*n*=15)	4 (range: 2–4)	2 (range: 1–4)	2 (range: 1–4)	**0.001****	0.339**
Median dysphagia score (*n*=16)	33 (range: 9–45)	37 (range: 15–45)	45 (range: 10–45)	0.507**	0.445**

GIQLI = Gastrointestinal Quality of Life Index; SD = standard deviation
*paired t-test; **related samples Wilcoxon signed-rank test

Table 6 Factors for risk of recurrence

Characteristic	*p*-value	
	Univariate regression	Multivariate regression
Age >70 years	0.020	0.017 (HR: 3.0, 95% CI: 1.2–7.4)
Tension in hiatal closure	0.050	0.032 (HR: 4.1, 95% CI: 1.1–14.7)
ASA grade ≥3	0.22	
Type IV hernia	0.29	
Body mass index >30kg/m^2	0.48	
Hiatal size 'very large'	0.53	
Hernia size ≥75%	0.65	
Male sex	0.72	
≥4 stitches in hiatus	0.97	

HR = hazard ratio; CI = confidence interval; ASA = American Society of Anesthesiologists

Endoscopic surveillance suggested oesophagitis was uncommon in our cohort (5%) compared with other large series.[14,15] In contrast to this, the prevalence of gastroparesis (as evidenced by the presence of gastric contents after fasting for endoscopy) was higher among our patients (19%). This parameter has not been reported well in other studies, however, and is therefore an avenue for further research.

Age >70 years and estimated tension were the only predictors of recurrence. Data for some cases were missing for tension (16%), BMI (29%) and ASA grade (30%). Conversely, it has been reported that younger and obese patients are more likely to experience recurrence.[12] However, the series are not comparable owing to differences in age (69 vs 63 years) and weight loss between the study cohorts.

During operations where tension was noted (n=7), the pneumoperitoneum was reduced to 8mmHg and the liver retractor was loosened to assist in the recruitment of the left diaphragm. It may be worth selecting this subgroup of patients for further measures to prevent recurrence. Releasing incisions in the diaphragm may be utilised[13] or mesh.[3,16]

Routine use of biological mesh in a large randomised controlled trial (RCT) did not show a reduction in the incidence of recurrence.[17] Another very small RCT of mesh in patients with large (8cm) hiatal defects did show a significant reduction in recurrence (0% vs 20% at 40 months).[16] This was perhaps an inverse finding because the 'no mesh' group results were poor. The efficacy of mesh buttressed repair remains uncertain. Reoperation was required in 3% of our cases so only a small proportion of patients treated with mesh may benefit. On the other hand, if mesh were used routinely, the risk of mesh related complication would be present in 97%.

The prospective studies of primary mesh hiatus repair reported no complications at long-term follow-up.[18–21] Nevertheless, reoperation was noted to be highly morbid, major resection at revision being required frequently. Recurrent hernias appear to be largely asymptomatic[12,15,17,22–24] and did not affect QoL in our series.

The reporting of recurrence has not been standardised, some not reporting recurrence of <2cm.[17] Using such criteria, our series would have a recurrence rate of only 5%. Other series only report symptomatic (ie not objective) recurrence, leading to difficult comparison.[25,26]

Recurrence in this cohort affected QoL at early follow-up review but not later. Early and later recurrence may have a different symptom profile or severity. Large recurrence had been detected in two patients by four months[6] and has been observed in five further patients since then. Two reoperations were performed during the study period of the initial report[6] and only one reoperation has been carried out during the later follow-up period. This difference was not significant but may represent different causation. The natural history of small recurrence is not known but it is possibly benign.[27]

Compared with preoperative scores, overall QoL and reflux scores remained significantly improved at 27 months, consistent with other reports of GHH repair.[10,12,13] Both the GIQLI and modified Visick scores improved, and did not change over time despite 24% of patients developing recurrence. Symptomatic outcome therefore appears durable.

Dysphagia has been assessed in two studies after surgery, using different reporting techniques and methodology.[12,13] Aly *et al* performed massive hiatus hernia repair without mesh, using posterior cardiopexy and predominantly 360° fundoplication in 100 patients.[12] At four years, 23% of patients developed recurrence, with 10% of all patients developing recurrence of >2cm and 7% having reoperation for recurrence or dysphagia. Dysphagia was recorded using a ten-point scale and was examined in a subgroup of patients who had significant preoperative dysphagia. In these 51 patients, the dysphagia scores improved from 6.1 to 1.5 (p<0.001). The analysis was different from that in our study and the results are therefore not comparable.

Andujar *et al* compared QoL in 166 patients with GHHs repaired without mesh, predominantly by 360° fundoplication (8.4% had gastropexy only).[13] Recurrent hernias were found in 25% of cases (5% large) but symptoms remained improved at 24 months. Early reoperation (7 months) was performed in 6% of patients.

A 360° fundoplication was chosen in this series as partial fundoplication has been associated with recurrent reflux.[28] Nevertheless, total fundoplication can be associated with a higher rate of reoperation[28] and dysphagia.[29] The three reoperations in this series, however, were for larger recurrences with resultant dysphagia. Barium swallow in these patients showed acute angulation at the GOJ, perhaps peculiar to the cardiopexy technique.

Oesophagitis was uncommon (5%), reflecting the use of total fundoplication. Poor gastric emptying is known to be associated with hiatal hernia.[30] Longer follow-up study is needed to assess whether postoperative food retention is a

temporary phenomenon related to surgery and vagal dysfunction or a permanent phenomenon.

The prevalence of Barrett's oesophagus was 27%. This confirms observations that there is a strong association between hiatal hernia and Barrett's oesophagus,[31–33] and suggests that endoscopy would be wise in this group of patients.

Conclusions

The composite fundoplication-cardiopexy technique led to sustained improvements at a median of 1,207 days in overall QoL and reflux but not dysphagia. Recurrence was predominantly small and relatively asymptomatic, the rates were comparable with those in other reports and reoperation was required infrequently. Patients with a recurrent hernia had symptoms similar to those with anatomically intact repairs. The risk factors of older age and tension in the repair may lead to consideration of alternative selective approaches to surgery in this small subgroup; however, it is unknown whether this would significantly affect reoperation rates. These figures cannot support a routine repair with mesh but perhaps a tailored approach could be evaluated for an identifiable higher risk group.

References

1. Watson DI, Devitt PG, Jamieson GG. The changing face of treatment for hiatus hernia and gastro-oesophageal reflux. *Gut* 1999; **45**: 791–792.
2. Swanstrom LL, Marcus DR, Galloway GQ. Laparoscopic Collis gastroplasty is the treatment of choice for shortened esophagus. *Am J Surg* 1996; **171**: 477–481.
3. Oelschlager BK, Pellegrini CA, Hunter J *et al*. Biologic prosthesis reduces recurrence after laparoscopic paraesophageal hernia repair: a multicenter, prospective, randomized trial. *Ann Surg* 2006; **244**: 481–490.
4. Watson DI, Devitt PG, Smith L, Jamieson GG. Anterior 90° partial vs Nissen fundoplication – 5 year follow-up of a single-centre randomised trial. *J Gastrointest Surg* 2012; **16**: 1,653–1,658.
5. D'Netto TJ, Falk GL. A technique for the laparoscopic repair of paraoesophageal hernia without mesh. *J Gastrointest Surg* 2014; **18**: 851–857.
6. Gibson SC, Wong SC, Dixon AC, Falk GL. Laparoscopic repair of giant hiatus hernia: prosthesis is not required for successful outcome. *Surg Endosc* 2013; **27**: 618–623.
7. Rijnhart-De Jong HG, Draaisma WA, Smout AJ *et al*. The Visick score: a good measure for the overall effect of antireflux surgery? *Scand J Gastroenterol* 2008; **43**: 787–793.
8. Eypasch E, Williams JI, Wood-Dauphinee S *et al*. Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. *Br J Surg* 1995; **82**: 216–222.
9. Dakkak M, Bennett JR. A new dysphagia score with objective validation. *J Clin Gastroenterol* 1992; **14**: 99–100.
10. Furnée EJ, Draaisma WA, Simmermacher RK *et al*. Long-term symptomatic outcome and radiologic assessment of laparoscopic hiatal hernia repair. *Am J Surg* 2010; **199**: 695–701.
11. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996; **17**: 343–346.
12. Aly A, Munt J, Jamieson GG *et al*. Laparoscopic repair of large hiatal hernias. *Br J Surg* 2005; **92**: 648–653.
13. Andujar JJ, Papasavas PK, Birdas T *et al*. Laparoscopic repair of large paraesophageal hernia is associated with a low incidence of recurrence and reoperation. *Surg Endosc* 2004; **18**: 444–447.
14. Poncet G, Robert M, Roman S, Boulez JC. Laparoscopic repair of large hiatal hernia without prosthetic reinforcement: late results and relevance of anterior gastropexy. *J Gastrointest Surg* 2010; **14**: 1,910–1,916.
15. Hashemi M, Peters JH, DeMeester TR *et al*. Laparoscopic repair of large type III hiatal hernia: objective followup reveals high recurrence rate. *J Am Coll Surg* 2000; **190**: 553–560.
16. Frantzides CT, Madan AK, Carlson MA, Stavropoulos GP. A prospective, randomized trial of laparoscopic polytetrafluoroethylene (PTFE) patch repair vs simple cruroplasty for large hiatal hernia. *Arch Surg* 2002; **137**: 649–652.
17. Oelschlager BK, Pellegrini CA, Hunter JG *et al*. Biologic prosthesis to prevent recurrence after laparoscopic paraesophageal hernia repair: long-term follow-up from a multicenter, prospective, randomized trial. *J Am Coll Surg* 2011; **213**: 461–468.
18. De Moor V, Zalcman M, Delhaye M, El Nakadi I. Complications of mesh repair in hiatal surgery: about 3 cases and review of the literature. *Surg Laparosc Endosc Percutan Tech* 2012; **22**: e222–e225.
19. Parker M, Bowers SP, Bray JM *et al*. Hiatal mesh is associated with major resection at revisional operation. *Surg Endosc* 2010; **24**: 3,095–3,101.
20. Stadlhuber RJ, Sherif AE, Mittal SK *et al*. Mesh complications after prosthetic reinforcement of hiatal closure: a 28-case series. *Surg Endosc* 2009; **23**: 1,219–1,226.
21. Tatum RP, Shalhub S, Oelschlager BK, Pellegrini CA. Complications of PTFE mesh at the diaphragmatic hiatus. *J Gastrointest Surg* 2008; **12**: 953–957.
22. Watson DI, Thompson SK, Devitt PG *et al*. Laparoscopic repair of very large hiatus hernia with sutures versus absorbable mesh versus nonabsorbable mesh: a randomized controlled trial. *Ann Surg* 2015; **261**: 282–289.
23. Targarona EM, Grisales S, Uyanik O *et al*. Long-term outcome and quality of life after laparoscopic treatment of large paraesophageal hernia. *World J Surg* 2013; **37**: 1,878–1,882.
24. Luketich JD, Nason KS, Christie NA *et al*. Outcomes after a decade of laparoscopic giant paraesophageal hernia repair. *J Thorac Cardiovasc Surg* 2010; **139**: 395–404, 404.e1.
25. Davis SS. Current controversies in paraesophageal hernia repair. *Surg Clin North Am* 2008; **88**: 959–978.
26. Draaisma WA, Gooszen HG, Tournoij E, Broeders IA. Controversies in paraesophageal hernia repair: a review of literature. *Surg Endosc* 2005; **19**: 1,300–1,308.
27. Le Page P, Furtado R, Hayward M *et al*. Durability of giant hiatus hernia repair in 455 patients over 20 years. *Ann R Coll Surg Engl* 2015; **97**: 188–193.
28. Engström C, Cai W, Irvine T *et al*. Twenty years of experience with laparoscopic antireflux surgery. *Br J Surg* 2012; **99**: 1,415–1,421.
29. Broeders JA, Mauritz FA, Ahmed Ali U *et al*. Systematic review and meta-analysis of laparoscopic Nissen (posterior total) versus Toupet (posterior partial) fundoplication for gastro-oesophageal reflux disease. *Br J Surg* 2010; **97**: 1,318–1,330.
30. Donovan IA, Harding LK, Keighley MR *et al*. Abnormalities of gastric emptying and pyloric reflux in uncomplicated hiatus hernia. *Br J Surg* 1977; **64**: 847–848.
31. Andrici J, Tio M, Cox MR, Eslick GD. Hiatal hernia and the risk of Barrett's esophagus. *J Gastroenterol Hepatol* 2013; **28**: 415–431.
32. Sgouros SN, Mpakos D, Rodias M *et al*. Prevalence and axial length of hiatus hernia in patients, with nonerosive reflux disease: a prospective study. *J Clin Gastroenterol* 2007; **41**: 814–818.
33. Cameron AJ. Barrett's esophagus: prevalence and size of hiatal hernia. *Am J Gastroenterol* 1999; **94**: 2,054–2,059.

JSCR Journal of Surgical Case Reports

Journal of Surgical Case Reports, 2015;7, 1–2

doi: 10.1093/jscr/rjv087
Case Report

CASE REPORT

Massive hiatus hernia complicated by jaundice

Ruelan V. Furtado[1], Trevor J. D'Netto[2], Henry C. Hook, Gregory L. Falk[1,2,3,4,5,*], and SarahJayne Vivian[5]

[1]Upper GI Surgery, Concord Repatriation General Hospital, Concord, Australia, [2]Sydney Adventist Hospital, Wahroonga, Australia, [3]University of Sydney, Sydney, Australia, [4]Macquarie University, Sydney, Australia, and [5]Sydney Heartburn Clinic, Lindfield, Australia

*Correspondence address. Suite 29, 12-18 Tryon Road, Lindfield, NSW 2070, Australia. Tel: +61-2-9745-1099; Fax: +612-9416-2907; E-mail: sydney.heartburn@gmail.com

Abstract

Giant para-oesophageal hernia may include pancreas with pancreatic complication and rarely jaundice. Repair is feasible and durable by laparoscopy. Magnetic resonance cholangiopancreatography is diagnostic.

INTRODUCTION

Herein reported a patient presenting with jaundice ultimately proving caused by a giant hiatus hernia also containing pancreas, and repaired successfully by laparoscopy.

CASE REPORT

A 59-year-old farmer presented with pain and obstructive jaundice. There were two recent episodes of post-prandial chest pain and vomiting with regurgitation of retained food. There was a history of early satiety, non-progressive dysphagia and significant weight loss in preceding months. There was no chest pain suggesting gastric volvulus.

The bilirubin was 158 µmol per litre and the alkaline phosphatase 751 IU/l, gamma glutamyl transferase (GGT) 1560 IU/l, aspartate aminotransferase 110 IU/l, and there was a normocytic anaemia (haemoglobin 130 3G/L). Computed tomography (CT) scan showed a massive hiatus hernia (MHH) containing duodenum and pancreas, and intra- and extra-hepatic biliary dilatation. The bile duct was not obtained at endoscopic retrograde cholangiopancreatography (ERCP), and the ampulla was normal. Magnetic resonance cholangiopancreatography (MRCP) showed a dilated biliary tree with axis deviation of the common bile duct (CBD) causing obstruction and kinking and proximal dilatation, where it entered the hiatal opening (Fig. 1).

At laparoscopy, the pancreas was seen entering the hiatus hernia (Fig. 2). Dissection of the sack allowed reduction in all hernia contents. The oesophagus was mobilised into the mediastinum, and the cardia was drawn without tension into the abdomen. Posterior and anterior repair of the hiatus was performed with 0 Ethibond. Total fundoplication and cardiopexy were performed as described by D'Netto *et al.* [1]. The patient left hospital 48 h after the procedure taking a full fluid diet. The bilirubin progressively returned to normal over 3 weeks. At 3-year follow-up, there were no symptoms and barium meal showed no recurrence.

DISCUSSION

Hiatus hernia is graded in four types. Type 1 sliding, Type 2 pure para-oesophageal, Type 3 mixed para-oesophageal and Type 4 mixed para-oesophageal with another organ also herniated in the chest (usually colon). Affected patients frequently may present with symptoms of early satiety, dysphagia, atypical chest pain, dyspnoea and iron deficiency anaemia [2].

Received: April 21, 2015. **Revised:** May 12, 2015. **Accepted:** June 26, 2015

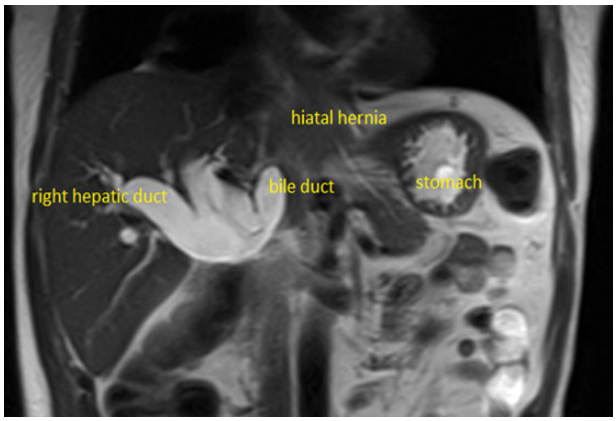


Figure 1: MRCP: biliary dilatation, kinking CBD on the hiatus.

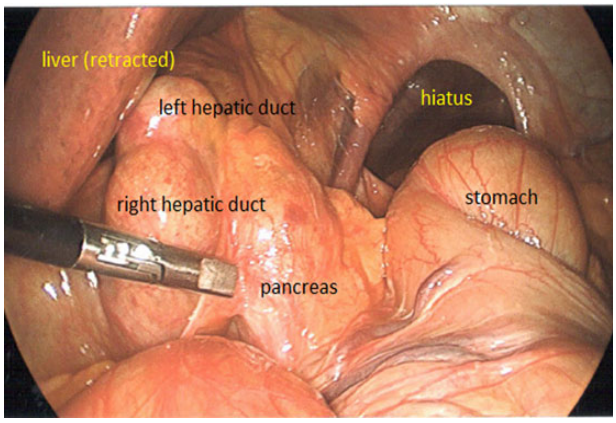


Figure 2: Intraoperative: pancreas seen herniated through hiatus. CBD dilated.

Incarceration of the pancreas is rare; however, pancreatitis has been reported as a presenting symptom due to obstruction of the duct of Wirsung [3].

This case illustrates an unusual cause of jaundice and the feasibility of repair by laparoscopy even when the pancreas is present in the chest [4]. Diagnosis was greatly facilitated by magnetic resonance imaging (MRI)/MRCP, and ERCP was technically difficult due to the position of the duodenum. The relationship between the hiatus, hernia and bile duct was well visualised confirming clinical suspicion. Occasional reports are present in the literature of pancreatic herniation causing jaundice in MHH [5–7].

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. D'Netto TJ, Falk GL. A Technique for the laparoscopic repair of paraoesophageal hernia without mesh. *J Gastrointest Surg* 2014;**18**:851–7.
2. Dean C, Etienne D, Carpentier B, Gielecki J, Tubbs RS, Loukas M. Hiatal hernias. *Surg Radiol Anat* 2012;**34**:291–9. doi:10.1007/s00276-011-0904-9.
3. Boyce K, Campbell W, Taylor M. Acute pancreatitis secondary to an incarcerated paraoesophageal hernia: a rare cause for a common problem. *Clin Med Insights Case Rep* 2014;**7**:25–7. doi:10.4137/CCRep.S13079. Received.
4. Gibson SC, Wong SC, Dixon AC, Falk GL. Laparoscopic repair of giant hiatus hernia: prosthesis is not required for successful outcome. *Surg Endosc* 2013;**27**:618–23.
5. Llaneza PP, Salt WB, Partyka EK. Extrahepatic biliary obstruction complicating a diaphragmatic hiatal hernia with intrathoracic gastric volvulus. *Am J Gastroenterol* 1986;**81**:292–4.
6. Lamouliatte H, Bernard PH, Lefebvre P, Boulard A, Arnal JC, Saric J, et al. Hiatal hernia with intrathoracic gastric volvulus as a rare cause of biliary obstruction. *Gastroenterol Clin Biol* 1992;**16**:89–91.
7. Caldeiro JC, Curcio A, Gigena VC, Barbarosa G. Choledochal semi volvulus with jaundice due to hiatal hernia. Initial percutaneous management. *Acta Gastroenterol Latinoam* 2001;**31**:329–32.

RCS ADVANCING SURGICAL STANDARDS

UPPER GI SURGERY

Ann R Coll Surg Engl 2015; **97:** 188–193
doi 10.1308/003588414X14055925060839

Durability of giant hiatus hernia repair in 455 patients over 20 years

PA Le Page[1], R Furtado[1], M Hayward[2], S Law[2], A Tan[2], SJ Vivian[3], H Van der Wall[4], GL Falk[1,2,3]

[1]Concord Repatriation General Hospital, NSW, Australia
[2]University of Sydney, NSW, Australia
[3]Sydney Heartburn Clinic, Lindfield, NSW, Australia
[4]Concord Nuclear Imaging, NSW, Australia

ABSTRACT

INTRODUCTION The surgical management of symptomatic giant hiatus hernia (GHH) aims to improve quality of life (QoL) and reduce the risk of life threatening complications. Previous reports are predominantly those with small sample sizes and short follow-up periods. The present study sought to assess a large cohort of patients for recurrence and QoL over a longer time period.

METHODS This was a follow-up study of a prospectively collected database of 455 consecutive patients. Primary repair of GHH was evaluated by endoscopy/barium meal for recurrence and a standardised symptom questionnaire for QoL. Recurrence was assessed for size, elapsed time, oesophagitis and symptoms.

RESULTS Objective and subjective review was achieved in 91.9% and 68.6% of patients. The median age was 69 years (range: 15–93 years) and 64% were female. Laparoscopic repair was completed in 95% (mesh in 6% and Collis gastroplasty in 7%). The 30-day mortality rate was 0.9%. The proportion of patients alive at five and ten years were 90% and 75% respectively. Postoperative QoL scores improved from a mean of 95 to 111 ($p<0.01$) and were stable over time (112 at 10 years).

The overall recurrence rate was 35.6% (149/418) at 42 months; this was 11.5% (48/418) for hernias >2cm and 24.2% (101/418) for <2cm. The rate of new recurrence at 0–1 years was 13.7% (>2cm = 3.4%, <2cm = 10.3%), at 1–5 years it was 30.8% (>2cm = 9.5%, <2cm = 21.3%), at 5–10 years it was 40.1% (>2cm = 13.8%, <2cm = 26.3%) and at over 10 years it was 50.0% (>2cm = 25.0%, <2cm = 25.0%). Recurrence was associated with oesophagitis but not decreased QoL. Revision surgery was required in 4.8% of cases (14.8% with recurrence). There were no interval major GHH complications.

CONCLUSIONS Surgery has provided sustained QoL improvements irrespective of recurrence. Recurrence occurred progressively over ten years and may predispose to oesophagitis.

KEYWORDS

Hiatal hernia – Gastro-oesophageal reflux – Laparoscopy – Fundoplication – Quality of life – Patient outcome assessment

Accepted 13 October 2014

CORRESPONDENCE TO

Philip Le Page, E: phillepage@yahoo.com.au

It is generally accepted in surgical circles that symptomatic giant hiatus hernias (GHHs) should undergo elective surgical repair given the risks of non-operative management.[1–3] A recent (and large) population-based observational study identified a 16.4% risk of death when hospitalised symptomatic patients are treated conservatively.[2] Patients are often elderly and frail,[4] and so a balance of surgical risk and life expectancy is required when considering surgical repair. There is, however, ongoing uncertainty, in part owing to the lack of long-term follow-up studies in regard to the natural history of the condition and the durability of repair and symptom improvement.

Ideally, the surgical repair of a GHH should be associated with a low morbidity and low risk of recurrence, favourable postoperative quality of life (QoL) indices, low reoperation rates and prevention of interval hiatus hernia complications. Recurrence rates of up to 66% have been reported.[5,6] As a result, numerous techniques have evolved with the aim of reducing recurrence rates. These techniques have included mesh hiatal repair[7] and Collis gastroplasty.[8,9] Reported recurrence rates have been variable and depend on the definition used[5,6] with some series excluding recurrence less than 2cm.[5,7,10]

QoL has been shown to be improved following repair.[10] This improvement is not only in gastrointestinal symptoms but also impacts on general wellbeing and cardiorespiratory symptoms.[11,12] There are, however, limited data on the durability of improvement and the prevention of

interval hiatus hernia complications.[8,13] The effect of recurrence on QoL has not been extensively investigated but recent studies suggest recurrence does not reduce symptomatic outcome.[5,14] The aim of our study was to assess the objective recurrence, QoL and oesophagitis over a long postoperative term in patients undergoing primary repair of GHH.

Methods

A prospectively populated database was maintained. The database was approved serially by an institutional ethics review board and consisted of consecutive patients referred from within the state of New South Wales, Australia, undergoing GHH repair in a single surgical practice between January 1991 and February 2012. Surgery was performed primarily by the senior author (GLF) or under his supervision. For a period of eight months in 2007 during the senior surgeon's leave of absence, locum surgeons performed operations at the same three tertiary referral hospitals and according to their usual practice. GHH was defined as type III or IV hiatus hernia with more than 50% of the stomach in the mediastinum or type II hiatus hernia with more than 30%,[1,10] based on preoperative barium meal and/or operative findings. Patients who had undergone previous surgery for GHH were excluded so that only primary repair was evaluated.

Surgical technique

Technical details have been published recently.[15,16] In brief, patients underwent complete removal of the hernia sac from the mediastinum and crural attachments. The oesophagus was mobilised in the mediastinum for sufficient length to allow tension free positioning of the gastro-oesophageal junction to a length of 2cm in the abdomen. The pillars of the crura were sutured deeply, including the central tendinous core (between 1 and 4 sutures being required), posteriorly and also frequently anteriorly. Calibration of the hiatus and the fundoplication was performed with a 52Fr bougie in female and a 56Fr bougie in male patients.

A Collis gastroplasty[17] was used for a period during an unpublished randomised study.[18] Mesh was largely used during the locum surgical practice period. Fundoplication was performed routinely, with its nature evolving. This was predominantly 360° and similar to that described by DeMeester *et al*,[19] and Rossetti and Hell.[20] After 2007, however, it incorporated an oesophagopexy and cardiopexy to the right crus as a 'composite repair'.

Review

Patient review was undertaken at six weeks and three months following surgery. Patients were asked subsequently to participate in follow-up consultations on a two-yearly basis. Attempts were made to contact all patients in June 2012 (census date) and a standardised QoL questionnaire was mailed to patients. This incorporated a Gastrointestinal Quality of Life Index (GIQLI) test after 1995,[21] gastro-oesophageal reflux disease assessment by modified Visick score[22] and DeMeester symptom profile,[23] a validated dysphagia score,[24] laryngopharyngeal reflux and overall satisfaction scores. The QoL questionnaire was self-administered or conducted by trained medical students or clinic staff. Objective follow-up review for recurrence was planned within one year of surgery and at census, often additionally being undertaken in the interim. Endoscopy was performed predominantly in the unit but for remote patients, regional endoscopy or a barium meal was undertaken.

Data management

The variables reviewed were age, operation date, laparoscopic or open surgery, fundoplication method, time to death, QoL, endoscopy and barium studies. Missing data points were obtained where possible from computerised patient records and local doctors by clinic staff, medical officers and medical students.

The primary outcomes assessed were objective recurrence of hiatus hernia and QoL. Recurrence of hiatus hernia was graded as total rate and size of >2cm or <2cm. Recurrence was also classified with respect to those hernias that had been identified by objective testing during the postoperative time periods 0–1, 1–5, 5–10 and >10 years. This was to enable comparison with previous published series[7,10] and to assess the patterns of recurrence. Recurrence was recorded at the date of objective tests. Barium images were reviewed by the unit radiologist if there was discordance in the reports. Individual patient QoL scores were averaged preoperatively and also within postoperative periods 0–1, 1–5, 5–10 and >10 years. Patients' results were censored at revision surgery. Presence of oesophagitis and Barrett's oesophagus were recorded from postoperative endoscopy.

Data were extracted to the software package STATISTICA version 8.0 (StatSoft, Tulsa, OK, US). QoL comparisons were analysed using Student's t-test for those patients who had paired data available and also using the Mann–Whitney U test for all unpaired data. Non-parametric data were analysed with Kruskal–Wallis analysis of variance and Student's t-tests. A p-value of <0.05 was considered statistically significant.

Results

GHH repair was performed in 475 patients. Primary repair was undertaken in 455 patients and they are the subject of this report. The median age was 69 years (range: 15–93 years) and 64% (n=292) were female.

Successful laparoscopic procedures were performed in 95% of patients. (Half of the open procedures had been performed during 1992–1996.) Composite fundoplication was used in 69% of patients, with DeMeester–Rossetti, Dor and Toupet techniques in 25%, 4% and 1% respectively. Mesh repair was undertaken in 27 patients (6%) and Collis gastroplasty in 33 patients (7%) as part of a randomised study, with no cases being performed for the inability to reduce the cardio-oesophageal junction into the abdomen. The mortality rate at 30 days was 0.9% (n=4, 3/4 undergoing surgery for acute strangulation). Survival data were

available for 98% (444/455 patients). The overall median follow-up duration was 32 months (range: 0–235 months). The overall survival rate was 90% at 5 years and 75% at 10 years with median survival being 192 months.

Recurrence

Anatomical follow-up was obtained in 418 patients (91.9%) and the median time to the most recent follow-up review was 13.2 months (range: 0–241 months). The recurrence rate at any postoperative time period was 35.6% (149/418), with a mean of 42 months following surgery (interquartile range: 6–60 months). Most recurrences were <2cm (101/149). The recurrence rate for larger hernias (>2cm) at any postoperative time period was 11.5% (48/418) while the recurrence rate for smaller hernias (<2cm) was 24.2% (101/418). A new diagnosis of recurrence (any size) continued to be identified from the first postoperative year to beyond ten years postoperatively (Table 1).

Revision

Revision operations were performed in 22 of the 149 patients with identifiable recurrence (14.8%) or 4.8% of the entire study population. No revision surgery was undertaken for strangulated recurrent hiatus hernia. These patients were predominantly those with >2cm recurrence (18 patients) and only four reoperations were performed when the recurrence was <2cm (all performed for significant symptoms attributable to recurrence). Reoperation occurred at a median of 23.3 months (range: 2 days – 90 months). Laparoscopic revision was undertaken in 12 patients. In those patients undergoing further objective testing after revision surgery, 39% had evidence of further recurrence (7/18: 3 following open and 4 following laparoscopic revision).

Oesophagitis and Barrett's oesophagus

Endoscopy was performed in 339 patients following surgery and 49 patients (14%) were found to have oesophagitis. Barrett's oesophagus was found in 94 patients (28% of those having endoscopy). Oesophagitis occurred in 29% (20/70) of patients with recurrence and in 11% (29/269) of those without (p=0.0004). The presence of oesophagitis was significantly different between the groups but it did not affect QoL scores.

Quality of life

At least one QoL questionnaire had been completed by 68.6% of patients following surgery (n=312). Overall postoperative QoL scores improved significantly. In paired analysis of the 136 patients having both pre and postoperative GIQLI tests, the preoperative mean score of 88 improved to 107 following surgery (mean improvement: 19, 95% confidence interval: 14–24, p<0.0001). In comparing unpaired data of individual QoL scores, postoperative improvement was identified for all parameters except the dysphagia score (Table 2). All scores remained stable beyond ten years postoperatively (Table 3). There was no difference in QoL scores in the presence of recurrence (Table 4).

Preoperative symptomatology on quality of life

Patients with the worst preoperative GIQLI score showed the greatest improvements in QoL scores after surgery. Those in the lowest preoperative GIQLI quartile showed a mean improvement of 67% and the second lowest quartile showed an improvement of 18%. Those in the second highest preoperative GIQLI quartile showed a mean improvement of 5% and the highest quartile showed a 5% worsening of GIQLI score.

Discussion

The patient group in this study was elderly and consistent with other series.[5,10,25] The longevity of our group was surprising, with 75% remaining alive at ten years. This may reflect the life expectancy increase in the Western world; at the average age of this group (69 years), the life expectancy is 16.0 years for men and 18.6 years for women.[26] It certainly demonstrates that hernia repair requires durability. Surgery appears to have been relatively safe in this series, with a low mortality, despite the elderly nature of the patient group and the low morbidity (8%) reported in an earlier report from our group.[16] The mortality rate at 30 days of 0.9% compares favourably with the natural history of symptomatic GHH, with a 16.4% mortality rate over 4 years in a study from 2009.[2]

Recurrence of hiatus hernia following surgery has been a consistent problem in many reports and has led to varied techniques of repair including the Collis gastroplasty, mesh hiatal repair and gastropexy procedures.[7,9,27] The overall

Table 1 Objective testing and recurrence rates stratified by time

	0–1 years	1–5 years	5–10 years	>10 years
Number having objective test*	321/455 (70.5%)	211/416 (50.7%)	80/299 (26.8%)	12/190 (12.6%)
Overall rate of new diagnosis of recurrence	13.7%	30.8%	40.1%	50.0%
Rate of new diagnosis of >2cm recurrence	3.4%	9.5%	13.8%	25.0%
Rate of new diagnosis of <2cm recurrence	10.3%	21.3%	26.3%	25.0%

*Denominator is the number of patients eligible for testing given that they had reached the respective follow-up period.

Table 2 Quality of life scores compared before and after surgery

Scoring test	Preoperative (*n*=147)			Postoperative (*n*=312)			*p*-value[a]	Change
	Median	Range	SD	Median	Range	SD		
GIQLI (0–144)[b]	95	28–133	23.0	111	33–144	23.0	**<0.01**	Improved
Symptoms	50	17–75	12.0	60	17–97	12.0	**<0.01**	Improved
Emotional	11	0–15	4.0	13	0–16	3.6	**<0.01**	Improved
Physical	15	0–26	6.4	17	0–28	6.2	**<0.01**	Improved
Social	13	2–16	3.6	14	0–33	3.5	**0.02**	Improved
Medical treatment	4	0–4	1.0	4	1–4	0.8	**<0.01**	Nil
Visick (0–4)[c]	3	0–4	1.0	2	0–4	0.9	**<0.01**	Improved
Dysphagia (0–45)[b]	37	6–45	11.1	39	0–45	9.4	0.18	Improved
DeMeester (0–12)[c]	8	0–12	3.0	4	0–12	4.2	**<0.01**	Improved
Laryngopharyngeal reflux (0–45)[c]	15	0–45	11.0	8	0–43	10.0	**<0.01**	Improved
Satisfaction (0–3)[b]	–	–	–	3	0–3	0.8	–	–

SD = standard deviation; GIQLI = Gastrointestinal Quality of Life Index
[a]Mann–Whitney U test; [b]Higher score reflects favourability; [c]Lower score reflects favourability

Table 3 Postoperative quality of life scores stratified by time

Scoring test	0–1 years (*n*=134, 29%)		1–5 years (*n*=109, 24%)		5–10 years (*n*=78, 17%)		>10 years (*n*=63, 14%)		*p*-value[a]
	Median	Range	Median	Range	Median	Range	Median	Range	
GIQLI (0–144)[b]	111	47–141	108	33–144	112	42–144	112	41–138	0.32
Symptoms	59	27–75	59	25–97	61	24–76	61	17–76	0.31
Emotional	13	1–16	13	0–16	13	3–16	13	3–16	0.49
Physical	17	3–28	16	0–28	19	4–28	18	1–26	0.07
Social	14	3–16	14	0–33	14	4–16	14	2.5–16	0.71
Medical treatment	4	1–4	4	1–4	4	1–4	4	1–4	0.27
Visick (0–4)[c]	2	1–4	2	0–4	2	0–4	2	0–4	0.36
Dysphagia (0–45)[b]	37	8–45	39	10–45	39	0–45	41	16–45	0.3
DeMeester (0–12)[c]	4	0–48	5	0–24	4	0–12	5	0–10	1
Laryngopharyngeal reflux (0–45)[c]	9	0–36	9	0–43	7	0–39	6	0–37	0.96
Satisfaction (0–3)[b]	3	0–4	3	0–3	3	0–4	3	0–3	0.57

GIQLI = Gastrointestinal Quality of Life Index
[a]Kruskal–Wallis analysis of variance; [b]Higher score reflects favourability; [c]Lower score reflects favourability

recurrence rate identified in this study of 35.6% is similar to that found in another large Australian series by Aly *et al*, who reported a 30% rate at a median of 4 years.[25] The largest published series of GHH, by Luketich *et al*, found a 15.7% recurrence rate at a median of 25 months in objective testing of hernias that were >2cm (or 10% of the stomach).[10]

In our series, there was a recurrence rate of 11.5% for hernias of this size. There were higher rates of small recurrent hiatus hernias (<2cm), which may lead to oesophagitis and symptoms. Although these may be of symptomatic consequence, it would appear unlikely that these would lead to revision surgery over the next 10–15 years given that only 4 patients with recurrences of small hernias required reoperation. No patients suffered an interval serious hiatus hernia complication.

Recurrence appeared to occur consistently over the years; the rate of new recurrences may even be increasing.

Table 4 Postoperative quality of life scores compared with and without hernia recurrence

Scoring test	No recurrence (*n*=333)		Recurrence <2cm (*n*=35)		Recurrence >2cm (*n*=21)		*p*-value[a]
	Median	Range	Median	Range	Median	Range	
GIQLI (0–144)[b]	108	33–144	114	67–142	108	64–132	0.33
Symptoms	59	17–101	61	30–101	61	45–73	0.24
Emotional	13	0–16	13	4–16	11	3.5–16	0.69
Physical	17	0–101	20	6–101	15	2–26	0.06
Social	14	0–33	14	6–101	14	5–16	0.32
Medical treatment	4	1–4	4	2–4	4	1–4	0.61
Visick (0–4)[c]	2	0–4	2	0–4	2	0–4	0.64
Dysphagia (0–45)[b]	38	0–45	39	19–45	45	18–45	0.21
DeMeester (0–12)[c]	4	0–12	6	0–10	6	0–11	0.08
Laryngopharyngeal reflux (0–45)[c]	8	0–43	9	0–37	6	0–32	0.98
Satisfaction (0–3)[b]	3	0–3	3	0–3	2	0–3	0.20

GIQLI = Gastrointestinal Quality of Life Index
[a]Kruskal–Wallis analysis of variance; [b]Higher score reflects favourability; [c]Lower score reflects favourability

The potential risk of bias in the long term must be realised, however, as patients with recurrence may be more likely to present for follow-up review. Our study had only a small proportion of patients undergoing objective testing beyond ten years. This reflects that many of these patients have become increasingly elderly, unfit and unwilling to undertake tests (especially if not symptomatic) or have died. Postoperatively, as age increased, patients became more difficult to locate and contact.

This study did not systematically utilise mesh or Collis gastroplasty and recurrence rates largely reflect a standard non-mesh approach. These data would indicate that other techniques are not necessary,[28] especially considering a study by our group published in 2013 of 100 patients undergoing a composite repair alone (2% and 7% symptomatic and non-symptomatic recurrence rate respectively, at a mean follow-up of 574 days).[16] There is also concern with the rare but problematic complication of mesh erosion and high risk of resection when refashioning in the presence of previous mesh.[29] Short oesophagus was probably rare in this study owing to the lack of stricture cases and nearly 30 years of availability of potent acid suppression, largely eliminating the short oesophagus. The Collis operations were done in a trial situation and did not reflect inability to reduce the cardio-oesophageal junction into the abdomen so no 'real' cases were found in the 455 procedures.

Reoperation rates for recurrence were low at 5% and occurred predominantly in patients with recurrence of hernias greater than 2cm. It would therefore appear prudent to continue to survey patients with recurrent hiatus hernia by both symptomatic and objective study to detect enlarging recurrent hernias.

It was disappointing that 39% of patients undergoing repeat repair relapsed again. This is in contrast to another report where only 3 of 26 patients recurred following revision.[30] However, this low reported rate may reflect early follow-up and later objective review is likely to report a higher rate. Another series reported 5 of 52 patients relapsing after undergoing repair for recurrence although objective follow-up methods and results were not reported.[31] The relatively high rate we identified should be considered in decision making regarding revision surgery, which is more challenging technically, more likely to be open and potentially more risky.[30] Importantly, reoperation was not necessary in this cohort for acute complications of GHH, which is one of the most important indications for primary surgery.

The symptomatic effect of recurrent hiatus hernia after repair is consistent with other large series where QoL appeared not to be affected following recurrence.[5,10,14] The results were not statistically significant, however, casting some uncertainty on this finding. Our study showed oesophagitis was significantly more common after recurrence. In addition, the protocol of undertaking postoperative endoscopy, which assessed recurrence and oesophagitis, interestingly identified a 28% rate of Barrett's oesophagus. Aly *et al* also identified a significant rate of Barrett's epithelium of 13% on preoperative endoscopy.[25] While preoperative endoscopy was performed too infrequently to allow comparison with postoperative endoscopy, these statistics do reflect the longstanding nature of reflux in some patients with GHH. It would seem prudent to perform postoperative endoscopy to detect a significant rate of Barrett's oesophagus, especially given the availability of effective endoscopic treatments of dysplasia, and oesophagitis manageable by medical therapy. The presence of oesophagitis did not influence QoL, possibly reflecting insensitivity of the oesophagus or the QoL measure.

Surgery led to a marked improvement in QoL. This was seen in GIQLI scores, reflux scores and laryngopharyngeal reflux scores. The effect extended beyond ten years. This has also been found in earlier studies.[5]

The longer-term objective data in our study were limited. Additionally, the postoperative objective and subjective tests were undertaken variably and sometimes inconsistently. These factors reduce the strength of our conclusions. The database did not contain morbidity data so this could not be reported. Nevertheless, a 2013 publication from our group prospectively analysing a recent cohort found an 8% rate of perioperative complications.[16]

Conclusions

There was an unexpected longevity in this cohort. Surgical repair of GHH provided a sustained improvement in QoL despite recurrence. There were no severe hiatus hernia related events following surgery, thereby reducing risks associated with GHH. Recurrence was associated significantly with an increased risk of oesophagitis. There was a high rate of Barrett's oesophagus, indicating that surveillance is important. More severely symptomatic patients benefit most from surgery. Mesh repair has not been required for adequate prolonged QoL improvement and short oesophagus appears infrequent.

Acknowledgement

The authors would like to acknowledge the contribution of Simon Gibson for assistance in designing the study.

References

1. Mitiek MO, Andrade RS. Giant hiatal hernia. *Ann Thorac Surg* 2010; **89**: S2168–S2173.
2. Sihvo EI, Salo JA, Räsänen JV, Rantanen TK. Fatal complications of adult paraesophageal hernia: a population-based study. *J Thorac Cardiovasc Surg* 2009; **137**: 419–424.
3. Wichterman K, Geha AS, Cahow CE, Baue AE. Giant paraesophageal hiatus hernia with intrathoracic stomach and colon: the case for early repair. *Surgery* 1979; **86**: 497–506.
4. Hazebroek EJ, Smith GS. Objective follow-up after laparoscopic repair of large type III hiatal hernia: assessment of safety and durability. *World J Surg* 2008; **32**: 1,563–1,564.
5. Dallemagne B, Kohnen L, Perretta S *et al.* Laparoscopic repair of paraesophageal hernia. Long-term follow-up reveals good clinical outcome despite high radiological recurrence rate. *Ann Surg* 2011; **253**: 291–296.
6. Hashemi M, Peters JH, DeMeester TR *et al.* Laparoscopic repair of large type III hiatal hernia: objective followup reveals high recurrence rate. *J Am Coll Surg* 2000; **190**: 553–560.
7. Oelschlager BK, Pellegrini CA, Hunter J *et al.* Biologic prosthesis reduces recurrence after laparoscopic paraesophageal hernia repair: a multicenter, prospective, randomized trial. *Ann Surg* 2006; **244**: 481–490.
8. Nason KS, Luketich JD, Awais O *et al.* Quality of life after Collis gastroplasty for short esophagus in patients with paraesophageal hernia. *Ann Thorac Surg* 2011; **92**: 1,854–1,860.
9. Collis JL. An operation for hiatus hernia with short esophagus. *J Thorac Surg* 1957; **34**: 768–773.
10. Luketich JD, Nason KS, Christie NA *et al.* Outcomes after a decade of laparoscopic giant paraesophageal hernia repair. *J Thorac Cardiovasc Surg* 2010; **139**: 395–404.
11. Carrott PW, Hong J, Kuppusamy M *et al.* Repair of giant paraesophageal hernias routinely produces improvement in respiratory function. *J Thorac Cardiovasc Surg* 2012; **143**: 398–404.
12. Zhu JC, Becerril G, Marasovic K *et al.* Laparoscopic repair of large hiatal hernia: impact on dyspnoea. *Surg Endosc* 2011; **25**: 3,620–3,626.
13. Zehetner J, DeMeester SR, Ayazi S *et al.* Laparoscopic versus open repair of paraesophageal hernia: the second decade. *J Am Coll Surg* 2011; **212**: 813–820.
14. Diaz S, Brunt LM, Klingensmith ME *et al.* Laparoscopic paraesophageal hernia repair, a challenging operation: medium-term outcome of 116 patients. *J Gastrointest Surg* 2003; **7**: 59–66.
15. D'Netto TJ, Falk GL. A technique for the laparoscopic repair of paraoesophageal hernia without mesh. *J Gastrointest Surg* 2014; **18**: 851–857.
16. Gibson SC, Wong SC, Dixon AC, Falk GL. Laparoscopic repair of giant hiatus hernia: prosthesis is not required for successful outcome. *Surg Endosc* 2013; **27**: 618–623.
17. Falk GL, Harrison RI. Laparoscopic cut Collis gastroplasty: a novel technique. *Dis Esophagus* 1998; **11**: 260–262.
18. Richardson MA, Cain GM, Adams IP, Falk GL. Laparoscopic cut Collis gastroplasty/fundoplication. *Can J Gastroenterol* 1998; **12(Suppl B)**: 383.
19. DeMeester TR, Bonavina L, Albertucci M. Nissen fundoplication for gastroesophageal reflux disease. *Ann Surg* 1986; **204**: 9–20.
20. Rossetti M, Hell K. Fundoplication for the treatment of gastroesophageal reflux in hiatal hernia. *World J Surg* 1977; **1**: 439–443.
21. Eypasch E, Williams JI, Wood-Dauphinee S *et al.* Gastrointestinal Quality of Life Index: development, validation and application of a new instrument. *Br J Surg* 1995; **82**: 216–222.
22. Visick AH. A study of the failures after gastrectomy. *Ann R Coll Surg Engl* 1948; **3**: 266–284.
23. DeMeester TR, Johnson LF. The evaluation of objective measurements of gastroesophageal reflux and their contribution to patient management. *Surg Clin North Am* 1976; **56**: 39–53.
24. Dakkak M, Bennett JR. A new dysphagia score with objective validation. *J Clin Gastroenterol* 1992; **14**: 99–100.
25. Aly A, Munt J, Jamieson GG *et al.* Laparoscopic repair of large hiatal hernias. *Br J Surg* 2005; **92**: 648–653.
26. Life Tables, States, Territories and Australia, 2010–2012. Australian Bureau of Statistics. http://www.abs.gov.au/AUSSTATS/abs@.nsf/DetailsPage/3302.0.55.0012010–2012 (cited December 2014).
27. Nason KS, Luketich JD, Witteman BP, Levy RM. The laparoscopic approach to paraesophageal hernia repair. *J Gastrointest Surg* 2012; **16**: 417–426.
28. Kelty CJ, Falk GL. The case against mesh repairs in hiatal surgery. *Ann R Coll Surg Engl* 2007; **89**: 479–481.
29. Stadlhuber RJ, Sherif AE, Mittal SK *et al.* Mesh complications after prosthetic reinforcement of hiatal closure: a 28-case series. *Surg Endosc* 2009; **23**: 1,219–1,226.
30. Juhasz A, Sundaram A, Hoshino M *et al.* Outcomes of surgical management of symptomatic large recurrent hiatus hernia. *Surg Endosc* 2012; **26**: 1,501–1,508.
31. Haider M, Iqbal A, Salinas V *et al.* Surgical repair of recurrent hiatal hernia. *Hernia* 2006; **10**: 13–19.

J Gastrointest Surg (2014) 18:851–857
DOI 10.1007/s11605-013-2397-9

HOW I DO IT

A Technique for the Laparoscopic Repair of Paraoesophageal Hernia Without Mesh

Trevor J. D'Netto · Gregory L. Falk

Received: 29 August 2013 / Accepted: 15 October 2013 / Published online: 19 November 2013

Abstract Laparoscopic paraoesophageal hernia repair is a challenging procedure, both in surgical technical difficulty and in prevention of recurrence, in the setting of operating on an older patient cohort with associated co-morbidities. However, modifications based on sound surgical principles can lead to better outcomes. This article describes and illustrates in detail the technique for the laparoscopic repair of paraoesophageal hernia without mesh with cardio-oesophageal junction fixation. The data and results of the study supporting this technique have been published previously by Gibson et al. (Surgical Endoscopy 27: 618–623, [2013]). The previously published article has reported on the numbers of patients, mean age, American Society of Anesthesiologists Physical Status Classification System, body mass index, duration of follow-up, complications, Visick scores and quality of life pre- and post-operatively. The principles of complete reduction of the hernia sac, preservation of both crura, mobilisation of the phreno-oesophageal ligament and phreno-gastric attachments, adequate mediastinal mobilisation of the oesophagus and the cardio-oesophageal junction into the abdomen without tension, preservation of both vagi, a tension-free crural repair including the fascial aspects adjacent to the diaphragm, an anterior hiatal repair in combination with the recognised posterior approximation, a loose fundoplication and a secure cardiopexy to the median arcuate ligament and multiple points of attachment; we have found leads to good operative results(Gibson et. al.) without the need for mesh. This article outlines in detail the operative technique guided by these principles with annotated intra-operative photographs illustrating the anatomy and procedure. The technique used by our team since March 2009 for the last 154 cases, based on the experience of an aggregate of 544 cases since 1999, we believe results in an acceptable level of symptomatic and anatomic recurrence without using mesh.

Keywords Hiatus hernia · Giant paraoesophageal hernia (PEH) · Laparoscopy · Gastro-oesophageal reflux · Surgical mesh · Cardiopexy · Fundoplication · Hernioplasty

Introduction

Repair of giant or massive hiatus hernia [defined as greater than 50 % of the stomach in the mediastinum (Fig. 1); a list of figures and titles is included at the end of this article] by laparoscopy has always been considered challenging. Surgical mesh repair has been entertained on multiple occasions in an attempt to reduce the recurrence rates and is controversial. This article describes the technique utilised in our series; the detailed data and results of which have been published previously [1,2] in Surgical Endoscopy titled "Laparoscopic repair of giant hiatus hernia: prosthesis is not required for successful outcome." The previously published article has reported on the numbers of patients, mean age, American Society of Anesthesiologists Physical Status Classification System, body mass index (BMI), duration of follow-up, complications, Visick scores and quality of life pre- and post-operatively. These results show low recurrence rates in medium-term (574 days) objective follow-up in 99 % of patients and *no* use of surgical mesh. Peri-operative complications and mortality have been acceptable. Improved quality of life and high levels of patient satisfaction have been obtained.

T. J. D'Netto (✉)
Macquarie University Hospital, Sydney Adventist Hospital,
Sydney, NSW, Australia
e-mail: dnetto@optusnet.com.au

G. L. Falk
Macquarie University Hospital, Sydney Adventist Hospital,
University of Sydney, Sydney, NSW, Australia
e-mail: sydney.heartburn@gmail.com

Selection

Patients with significant gastro-oesophageal symptoms[3] or dyspnoea[4] have been selected for management. Younger patients (assessed to have a life expectancy >20 years) with very large hiatus hernia and lesser symptoms have been repaired to

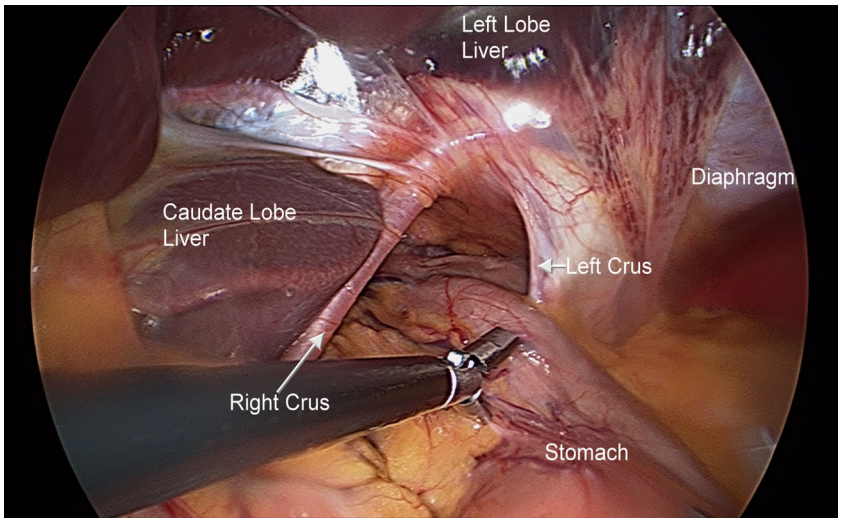


Fig. 1 Giant paraoesophageal hiatus hernia

reduce the risk of morbidity and mortality over the ensuing decades[3]. Patients generally did not describe severe levels of heartburn and regurgitation, but rather entrapment symptoms of early satiety, dysphagia, and atypical chest pain.[4] Occasional patients presented with multiple episodes of acute gastric volvulus. In the last 2 years, patients have been encouraged to lose weight down to a BMI of 32 and examined prior to surgery so that their abdomen in the recumbent position was at least flat and not bulging. All patients undergoing primary operation have been considered for laparoscopic repair. Routine investigation included barium upper gastrointestinal study or endoscopy and respiratory function testing and stress echocardiography. Patients are selected on symptoms and the above studies. In view of controversial results on the value of manometry, this is not routinely performed.

Surgery

Surgery was carried out under general anaesthesia using total intravenous anaesthesia techniques with the avoidance of nitrous oxide to lessen the risk of post-operative nausea and vomiting. The patient was positioned in the supine, lithotomy and reverse Trendelenburg position. Sequential calf compression, subcutaneous fractionated heparin and anti-thromboembolic stocking prophylaxis was used. Bladder catheterisation was not routine, but was performed if required for monitoring of other co-morbidities. The surgeon stood between the legs and the assistant on the left side of the patient.

Port Placement: a Five-Port Laparoscopic Method was Utilised[2]

A 10-mm optical entry port (Ethicon Endosurgery LLC, Guayno Puerto Rico USA) was inserted in the left medial rectus line 10 cm below the left subcostal margin and peritoneal access obtained under direct vision. Pneumoperitoneum was then achieved with carbon dioxide insufflation. A pressure of 12 cm water was used. Secondly, a Nathanson retractor (Cook Group Inc, Bloomington, IN) was inserted in the midline high epigastrium and positioned to provide a clear vision

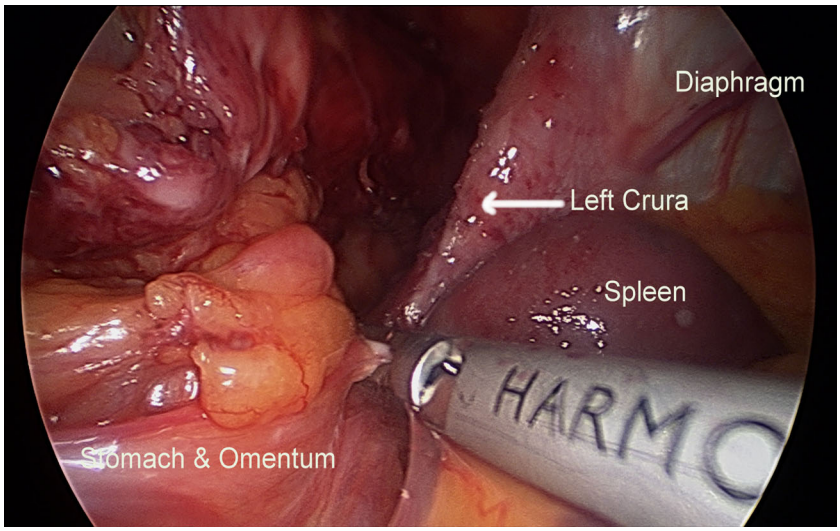


Fig. 2 Short gastric vessels divided

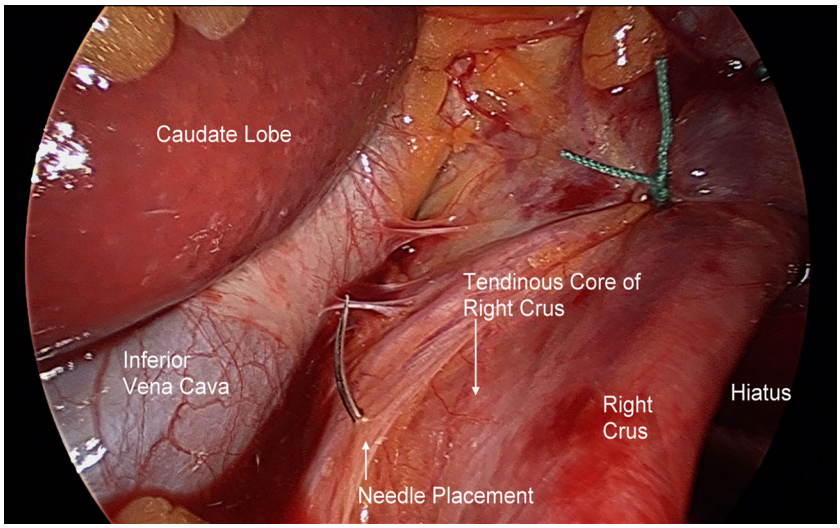


Fig. 3 Suture right crus, proximity IVC and caudate lobe

of the hiatus and diaphragm, while retracting the left lobe of the liver. Thirdly, an 8-mm port was inserted in the left anterior axillary line below the subcostal margin and 5 mm ports in the left flank and mid-right abdomen.

The harmonic scalpel was used for dissection (Ethicon Endosurgery, Johnson and Johnson, Cincinatti, USA). Haemostasis with this instrument was excellent and allowed ready dissection of the hernia sac. Surgery was carried out using a 0° laparoscope but was changed at times to 30° laparoscope for visualisation of the posterior left crural pillar, hiatus or short gastric vessels if necessary. Grasping instruments were 5 mm in diameter and had a large jaw surface area with pyramidal pattern grasping surfaces to avoid slippage and serosal damage to the organs when retracted. We have found a Babcock grasper to cause serosal injury due to its point pressure.

Dissection

Dissection was commenced by dividing the lesser sac and identifying the right pillar of the crus. The phreno-oesophageal ligament was then incised passing from the 9 o'clock position to the 3 o'clock position by division of the phreno-oesophageal membrane, identifying the oesophagus and anterior vagus nerve and allowed distraction of the large sac from the mediastinum. The phreno-oesophageal membrane was often not appreciable in large herniae, and instead, the sac was divided and entered at the point of attachment to the crura. If dissection was performed with meticulous haemostasis, good views and good lighting was obtained across the anterior oesophagus and enabled identification of both pleura.

Dissection in the mediastinum was performed inside the pillars of the crura by division of mediastinal structures using the harmonic scalpel. This was done without shredding or bleeding, as blood staining of the tissue led to poor visualisation of the anatomy partly due to loss of illumination. Blunt dissection was avoided. Slower dissection in the mediastinum allowed the insufflated gas to open planes in the loose areolar tissue and made separation of structures easier.

The sac was mobilised along its entirety, down to the base of both crural pillars until a full circumferential sac could be

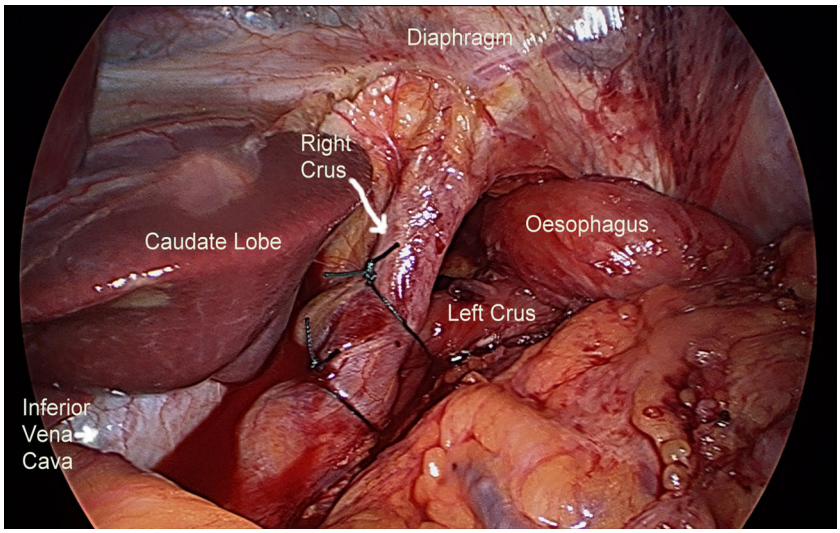


Fig. 4 Sutured right and left crura

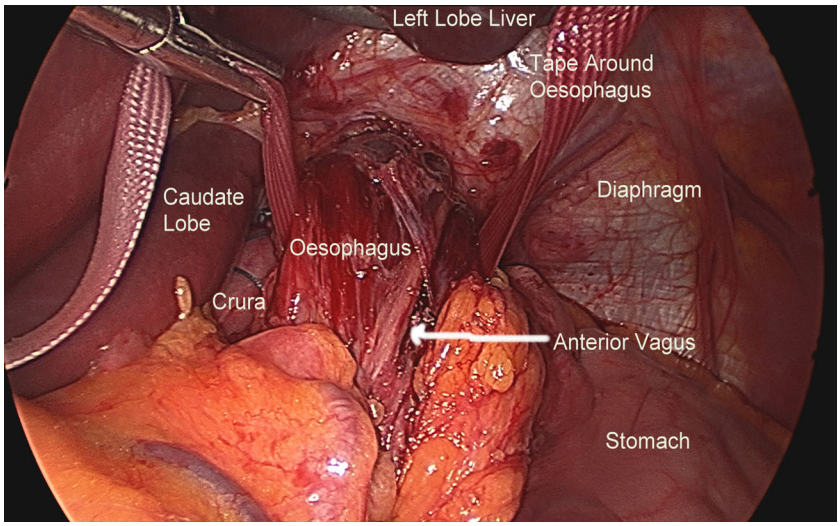


Fig. 5 Anatomy prior to fundoplication wrap

delivered out of the chest with the assistant's traction through the left flank port. It was a routine during this dissection that one or two of the upper short gastric vessels required division for identification of the posterior region of the left sac on the crural pillar (Fig. 2). The posterior vagus nerve was identified and retracted with the oesophagus.

Sac Removal

The sac was dissected away from the 'angle of His', often in several pieces, preserving the anterior vagus nerve and being mindful of the tortuous course of an elongated left gastric artery within the right sac material. There was often a large lipomatous posterior fat pad associated with the right sac component and involving the posterior vagus nerve, and this component was also carefully excised. Once the sac was removed, the oesophagus was easily encircled by a nylon tape and retracted into the abdomen.

Mediastinal Dissection

The assistant retracted the oesophagus caudally bringing the cardio-oesophageal junction towards the hiatus. Dissection alongside the anterior and posterior vagus nerves and the oesophagus was performed and it was often the vagus nerves which required mobilisation to allow the oesophagus and cardio-oesophageal junction to enter the abdomen without tension. Dissection of the oesophagus beyond the inferior pulmonary vein and often to the level of the carina was performed. It has not been necessary to perform a Collis procedure because with adequate dissection and mobilisation of the oesophagus, there has been a sufficient intra-abdominal, tension-free length of oesophagus. The pleura frequently met behind the oesophagus and was closely applied to the aorta and the vertebral bodies; therefore, a slower dissection with visualisation of this area avoided the issue of breaching the pleural space.[5] Should this occur a moderate tension pneumothorax (capnothorax),[6] without pulmonary damage can ensue,

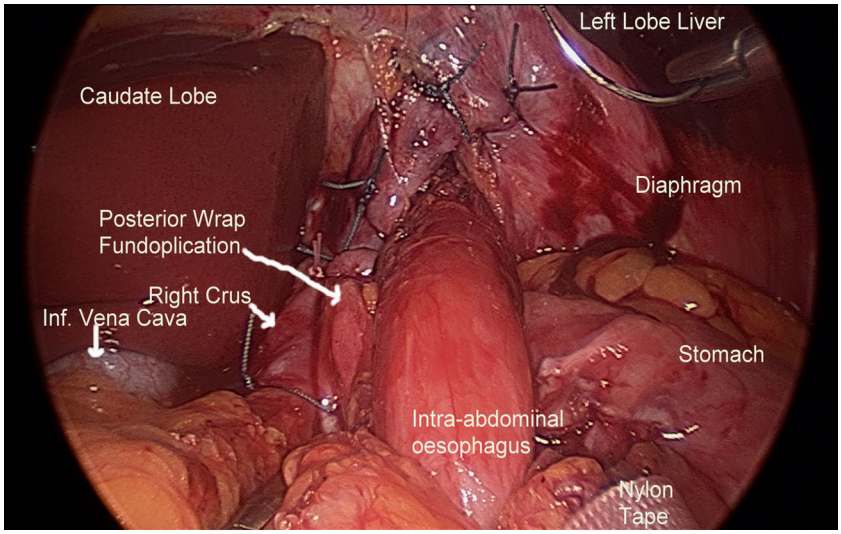


Fig. 6 Posterior fundoplication wrap and cardiopexy

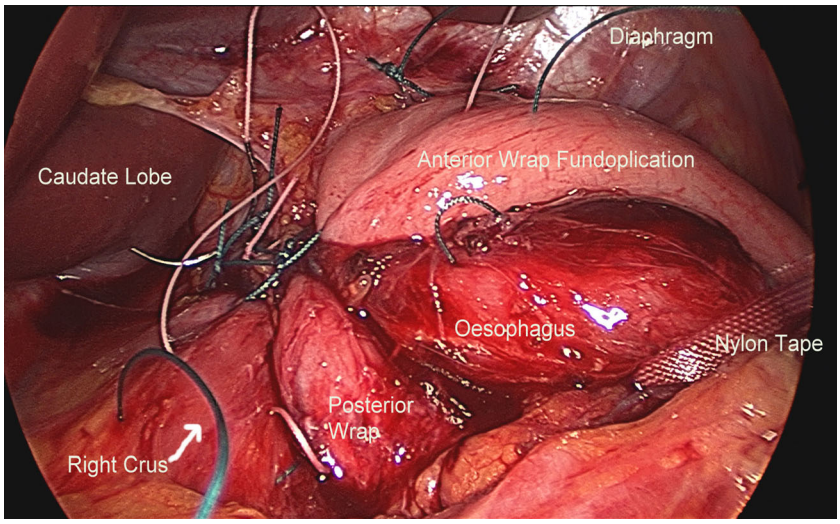


Fig. 7 Fundoplication wrap

sometimes leading to reduced cardiac output and blood pressure. This was managed laparoscopically by aspiration and decreased insufflation pressure, at times either having plugged the defect with a gauze ribbon (it was removed from the abdomen subsequently) or by applying a loop to the defect with a PDS Ethicon Endo loop. Anaesthetic intervention with pressor agents, positioning and increased inspiratory pressure was required in some cases.

Repair of the Hiatus

Repair of the hiatus was performed by placement of two to four posterior sutures of non-absorbable material (Ethibond-Ethicon, Johnson & Johnson) and anterior hiatus sutures in the central tendon of the diaphragm. This enabled recruitment of the dome-like left hemi-diaphragm, and therefore, no tension in the hiatus closure, as the left crus moved towards the more fixed right crus. Sutures were placed deeply to pick up the fascia and the tendinous core of the crus[7](Fig. 3) as described by RHR Belsey (and not the muscle fibres only) of both the left and right crura (Fig. 4), and in this situation, the right crus does not fray. Necessarily, the right crus sutures were close to the inferior vena cava. Surgical mesh repair was not required. Reduction in laparoscopic insufflation pressure and a reduction in the tension of the Nathanson retractor rostrally aided the tension-free hiatus repair (Fig. 5). It was important not to anteriorly displace the oesophagus to the point of angulation, but rather have it pass through from the mediastinum into the abdomen in a gentle curve. It was our view that undue angulation of the oesophagus leads to dysphagia.

Fundoplication and Gastropexy

The fixation and fundoplication were based upon the Menguy procedure.[8] The superior aspect of the posterior cardiopexy

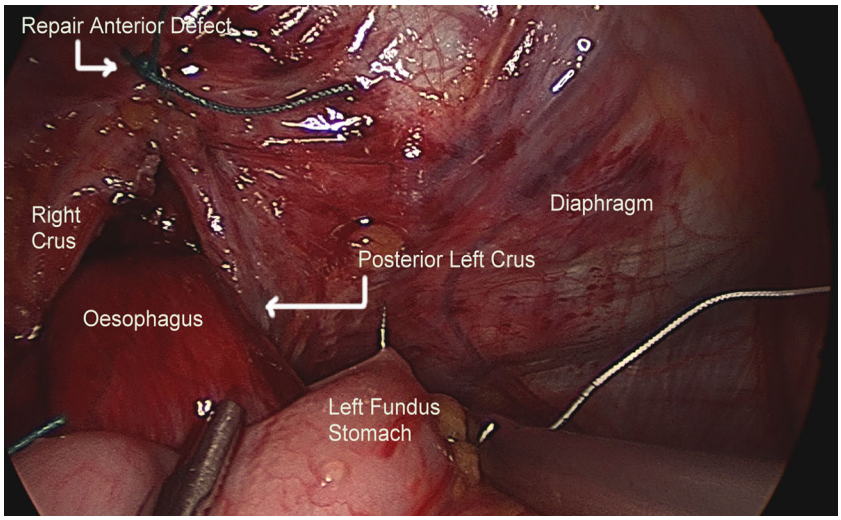


Fig. 8 Left fundus to posterior left crura

was passed around the oesophagus, ensuring there was no tension on the stomach or oesophagus so as to create a soft wrap. Two sutures incorporating generous 'bites' of the oesophagus and cardio-oesophageal junction, posterior fundus, median arcuate ligament and repaired crus were placed using 2/0 Ethibond (Fig. 6). These sutures were then tied. It was helpful to have sutures of different colours to differentiate the ends which were being tied. Total fundoplication was then completed by two sutures through the left-sided anterior fundus, posterior fundus and right crus, again with sutures of different colour and tied after placing both sutures initially (Fig. 7). Further sutures were placed attaching the left fundus to the posterior left crus (Fig. 8). All sutures were tied intracorporeally.

Completion

Local anaesthetic infiltration of the crural repair and port sites was utilised. A 56 French bougie in males or a 52 French bougie in females was used to check diaphragmatic and fundoplication tightness under direct vision. This was done because it was technically easier to suture and manipulate the needle in the extra space available in the absence of a bougie. A suture was rarely added or removed if the closure was too loose or too narrow to obtain the desired hiatal opening. Care was taken using Hurst Maloney tapered bougies to avoid oesophageal perforation (one in the total series). Capnothorax, if present, was managed by complete aspiration of carbon dioxide from the chest cavity and abdomen, and a chest X-ray was performed only if there was post-operative respiratory compromise. This was very infrequent. Wounds were closed with clips and redressed with transparent dressings at 48 h with simultaneous removal of clips. Patients were admitted to the intensive care unit only if necessary for co-morbidities. Post-operative analgesia aimed to avoid the use of opioids to reduce the risk of nausea and vomiting. No oral non-steroidal anti-inflammatory analgesia (NSAID) was used; however, per rectal, intramuscular or intravenous administration of NSAID was used if appropriate. The use of intravenous paracetamol was routine for the first 48 h.

Possible Complications

We have occasionally observed intra-operative ischemia of the upper pole of the spleen, close division of the upper short gastric vessels against the stomach, haematoma in the left lobe of the liver from the Nathanson retractor, haematoma in the fundoplication, transient elevated liver function tests secondary to the Nathanson retractor (always), bleeding from branches of the left gastric artery treated by harmonic scalpel or Endo loop (Ethicon Endo-Surgery) ligation. There is a theoretical risk of perforation of the oesophagus (one case in the series[1,2]) or stomach and vagal nerve damage. Division of the lesser omentum may divide a recurrent nerve to the pylorus and influence gastric emptying. Intra-operative pneumothorax (capnothorax) may occur. Little dysphagia has occurred after 6 weeks post-operatively. A small proportion has transient gastroparesis after surgery identified by food being present in the stomach at the post-operative endoscopy. There have been three deaths in the entire series; two with acute gastric volvulus and urgent operations, one with acute myocardial infarction and one with a mediastinal abscess many months following surgery. Morbidity has been low. Recurrence rates have been 2 % symptomatic and 5 % <2 cm asymptomatic. There have been no cases requiring mesh hernioplasty with this technique. There has been one re-operation for mediastinal abscess.

Conclusion

Laparoscopic surgery for paraoesophageal hernia has been performed in 544 patients since 1999, and this procedure describes the technique in the last 154 cases since March 2009. There has been substantial improvement in the quality of life and little new dysphagia.

Conflict of Interest Trevor J. D'Netto and Gregory L. Falk have no conflict of interest or financial ties to disclose.

References

1. Falk GL, Chan BM, Falk SE. Primary repair of giant hiatus hernia is satisfactory without mesh: early results of a method revisited. *J Laparoendosc Adv Surg Tech A*. 2012 Oct; 22(8): 748–52.
2. Gibson SC, Wong SK, Dixon AC, Falk GL. Laparoscopic repair of giant hiatus hernia: prosthesis is not required for successful outcome. *Surg Endosc* 2013 Feb; 27(2): 618–623
3. Sihvo EI, Salo JA, Rasenen JV, Rantanen TK. Fatal complications of adult paraoesophageal hernia: a population based study. *J Thorac Cardiovascular Surg* 2009; 137: 419–424.
4. Naoum C, Falk GL, Ng ACC, Lu T, Ridley L, Ing AJ, Kritharidesh, Yiannikas J. Left atrial compression and the mechanism of exercise impairment in patients with a large hiatal hernia. *J Am Coll Cardiol*. 2011; 58(15): 1624–1634.
5. D'Netto TJ, Falk GL, Phillips S. Laparoscopic images of pneumothorax in repair of massive hiatus hernia. *Aust N Z J Surg* 2012; 82(11): 848

6. Phillips S, Falk GL. Surgical tension pneumothorax during laparoscopic repair of massive hiatus hernia: a different situation requiring different management. *Anaesth Intensive Care* 2011; 39(6): 1120–3.
7. Jamieson GG. Surgery of the oesophagus. *Churchill Livingstone* 1988; Ch 25: Pg 257
8. Menguy R. Modified fundoplication which preserves the ability to belch. *Surgery* 1978; 84(3): 301–7

Comment

Laparoscopic repair of paraoesophageal hernia is the standard operative approach for our patients. Compared to open operation, post-operative complications were low, and length of stay in hospital was greatly shortened. Improved outcomes with a lower morbidity and mortality were obtained, and this technique has resulted in very acceptable recurrence rates.

IMAGES FOR SURGEONS

ANZJSurg.com

‘Pantaloon’ diaphragmatic hernia masquerading as a paraoesophageal hiatal hernia

A 51-year-old woman presented acutely with a strangulated, paraoesophageal hiatal hernia. Symptoms included worsened epigastric pain, regurgitation, post-prandial vomiting, nausea and anorexia. Esomeprazole (PPI) had given no relief. There was a history of obesity (body mass index of 31 kg/m^2 after recent weight loss) and a previous laparoscopic cholecystectomy.

The acute computed tomography (CT) scan (Fig. 1) and barium meal were reported as a paraoesophageal hernia with mesenteroaxial volvulus. At laparoscopy, there was a lax hiatus, which contained a moderate (<3 cm), sliding hernia. Further dissection showed an unsuspected, 4-cm hernial orifice posterolateral to the left crus that contained acutely incarcerated, inflamed fundus and omentum of approximately 250 mL. Two hernias were therefore identified on either side of the left crural pillar, effectively forming a ‘pantaloon’ (Fig. 2). This was not appreciated on preoperative imaging.

The hernial contents were reduced, but the sac of the Bochdalek hernia was firmly adherent to pleura, preventing safe reduction of the sac itself; however, the incarcerated, adherent contents were reduced. The defect was closed with multiple 0 Ethibond (Ethicon, Somerville, NJ, USA) sutures without tension. Tension was prevented by loosening of the liver retractor and reducing insufflation pressure, allowing anterior and posterior cruroplasties and repair of the Bochdalek hernia. A 360-degree fundoplication with caridiopexy completed the procedure (Fig. 3). The patient was discharged on day 4 without complication.

Bochdalek’s hernias develop as a result of incomplete fusion of the crural and costal components of the diaphragm, which develop in the fourth to sixth weeks of gestation. The usual presentation is in a paediatric patient with respiratory symptoms. Adults, on the other hand, tend to have abdominal complaints.[1]

In a radiological series of 13 138 adult patients, the incidence of asymptomatic hernias was 0.17%.[2] These occurred more frequently in women (77%) and were more common on the right (68%).

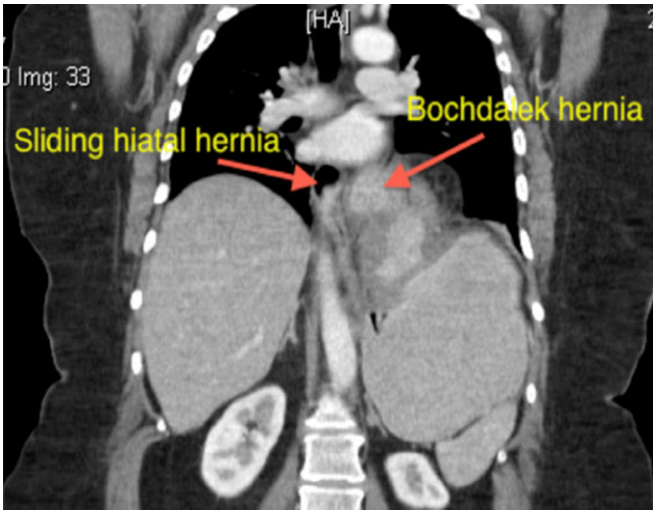


Fig. 1. Close inspection of the coronal section of the preoperative contrast-enhanced CT shows two distinct hernias.

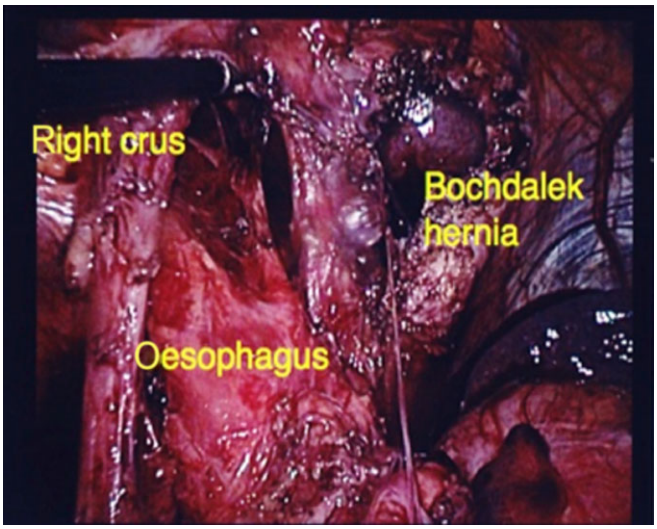


Fig. 2. View at laparoscopy after dissection of the hernial sacs shows an unsuspected orifice posterolateral to the left crus.

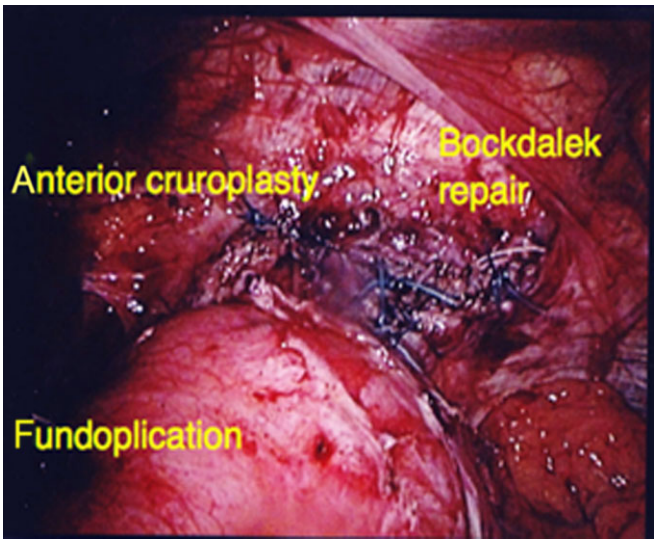


Fig. 3. A view at the end of the procedure shows the anterior part of the hiatal repair above the fundoplication. Laterally, the Bockdalek repair was completed without undue tension on the diaphragm.

In contrast, the majority clinically are left-sided.[1] This is the first case report of concurrent hiatal and congenital hernia repairs in a patient, who was initially thought to have a large paraoesophageal hiatus hernia.

References

1. Brown S, Horton J, Trivette E, Hofmann L, Johnson J. Bochdalek hernia in the adult: demographics, presentation, and surgical management. *Hernia.* 2011; **15**: 23–30.
2. Mullins M, Stein J, Saini S, Mueller P. Prevalence of incidental Bochdalek's hernia in a large adult population. *AJR Am. J. Roentgenol.* 2001; **177**: 363–6.

Ruelan Furtado, BSc, MBBS
Phillip Le Page, MBBS, FRACS
Gregory Falk, MBBS, FRACS
Concord Repatriation General Hospital, Sydney, New South Wales, Australia

doi: 10.1111/ans.12252

Surg Endosc (2008) 22:1625–1631
DOI 10.1007/s00464-007-9669-y

Evaluation of DualMesh for repair of large hiatus hernia in a porcine model

G. S. Smith · E. J. Hazebroek · R. Eckstein · H. Berry · W. M. Smith · J. R. Isaacson · G. L. Falk · C. J. Martin

Received: 4 May 2007 / Accepted: 4 October 2007 / Published online: 14 November 2007

Abstract
Background Prosthetic fascial grafts are frequently used for augmentation of cruroplasty in large hiatus hernia repair to decrease the chances of recurrence. Potential complications such as intraluminal erosion may be related to the constant movement of mesh and diaphragm over the outer surface of the esophagus. This study aimed to evaluate DualMesh for repair of large hiatal defects in a porcine model.
Methods In this study, 18 Landrace × large white × Duroc crossbred pigs underwent either primary hiatal repair or tension-free prosthetic repair using DualMesh (80 × 50 mm or 80 × 100 mm). The animals were killed at 3 or 28 weeks for macroscopic and histologic evaluation of the hiatal region and gastroesophageal junction.
Results All grafts had become encapsulated at 28 weeks, and the majority had filmy adhesions only to the visceral aspect. In all models, the esophagus moved freely over the cut edge of the prosthesis. No signs of intraluminal erosion were documented. At histologic examination, significant ingrowth was noted on the porous side of the mesh, whereas no defined mesothelial layer was identified on the capsule of the nonporous side.
Conclusion In this animal model of large hiatus hernia repair, DualMesh showed optimal characteristics in terms of host tissue incorporation on the porous side and absence of adhesions on the visceral side of the prosthesis. The absence of adhesions and intraluminal erosion in this study may provide reassurance to surgeons using mesh at the hiatus.

Keywords Hiatus hernia · Laparoscopic · Mesh repair · Porcine

G. S. Smith (✉) · E. J. Hazebroek · H. Berry
Department of Surgery, Royal North Shore Hospital, Level 2, Vindin House, St. Leonards, Sydney NSW 2065, Australia
e-mail: garetts@med.usyd.edu.au

R. Eckstein
Department of Anatomical Pathology, Royal North Shore Hospital, Sydney, Australia

W. M. Smith
The Faculty of Veterinary Science, The University of Sydney, Sydney, Australia

J. R. Isaacson · G. L. Falk
Department of Surgery, Concord Repatriation Hospital, Sydney, Australia

C. J. Martin
Department of Surgery, Nepean Hospital, Sydney, Australia

Various prosthetic fascial grafts have been used for augmentation of cruroplasty in large hiatus hernia repair to prevent recurrence, the rate of which is high after primary closure. Primary suture closure of the hiatal defect ignores the principles of fascial hernia repair because apposition at the margins of the defect, which usually consists of attenuated muscle, often is performed under tension.

A commonly used intraperitoneal fascial prosthesis is expanded polytetrafluoroethylene (ePTFE), which was introduced in the early 1970s as a venous graft [1]. DualMesh (W.L. Gore & Associates Inc. Newark, DE, USA) is an asymmetric ePTFE prothesis with one porous surface and one smooth surface. Descriptions of its use in the repair of large hiatus hernias usually are given in the context of case reports or selected cases from large series of primary repairs.

In one randomized control trial, Frantzides et al. [2] demonstrated reduction in the recurrence rate of hernias by the use of DualMesh to reinforce primary hernia repair. The majority of reports on the use of DualMesh describe

placement of the prosthesis cut edges at the level of the hiatal aperture and abutting the esophageal wall. The dynamic nature of the hiatal/cardioesophageal junction region has the potential therefore to result in erosion of the graft into the esophageal lumen. For this reason, a number of authors recommend avoiding the use of prostheses for hiatal repair.

DualMesh has been evaluated in a porcine model of ventral hernia repairs and found to elicit fewer adhesions when placed intraperitoneally than polypropylene [3]. No evaluation of DualMesh has been performed in a specific animal model of hiatal hernia. This study aimed to evaluate DualMesh used to repair large hiatal defects in a porcine model.

Materials and methods

A large hiatal hernia model was created by excising the left crural pillar and portion of the left hemidiaphragm in 18 Landrace × large white × Duroc crossbred pigs. The defects created were of two sizes: a standard size (40 × 30 mm) and a larger size (40 × 50 mm). In creating the larger defect, it was necessary to divide the left inferior pulmonary ligament to mobilize the lung away from the excised diaphragmatic portion.

After creation of the defect, closure was performed by either primary closure (n = 5) or tension-free DualMesh repair using either standard DualMesh (n = 7) or large DualMesh (n = 6). Primary closure was performed with interrupted braided polyester sutures (0 Ethibond; Ethicon, Johnson and Johnson International, Brussels, Belgium) spaced at 10-mm intervals and including 10 mm of diaphragmatic tissue in each bite. To assess a relation between total mesh surface and the development of adhesions, two sizes of DualMesh prosthetic patch were used to perform a tension-free repair: an 80 × 50-mm prostheses for the standard-sized defects and an 80 × 100-mm prosthesis for the larger defects. A semicircular defect was cut in the prosthesis to enable passage of the esophagus (Fig. 1a and b).

The patch was fixed to the margins of the defect with interrupted ePTFE sutures placed 8 mm from the edge of the mesh and 8 mm from the margins of the defects, providing approximately 16 mm of prosthesis/diaphragm overlap. Additional sutures were placed at the edge of the patch to prevent "curling" so that contact of the porous surface of the prosthesis with the underlying viscera could be avoided. At completion of the repair, the edge of the prosthesis abutted the posterior aspect of the esophagus.

Postoperatively, the animals were kept in single pens and subsequently in open group pens with yard access. The models were killed at 3 or 28 weeks.

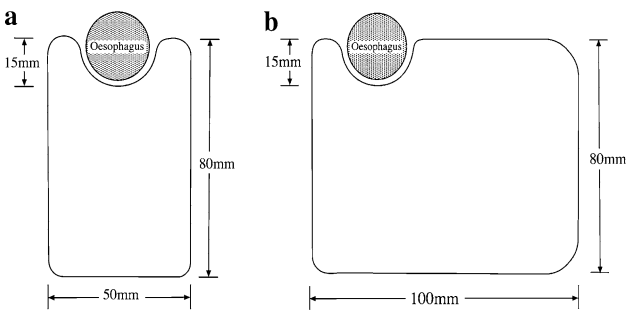


Fig. 1 (**a**) Standard-size prosthesis. (**b**) Larger-size prosthesis

Macroscopic evaluation

Postmortem, a thoracoabdominal window was created by excision of the inferior four ribs and musculature of the superior anterolateral abdominal wall. The thoracic cavity was inspected, and the presence of hernia or peritoneal sac was noted. The abdominal cavity was entered at the periphery of the diaphragm well away from the site of hiatal repair. The repairs were exposed, and the degree of viscera needed to repair adhesions was quantified using a previously reported scoring system [4] (Table 1).

The interface between the posterior aspect of the esophagus and the edge of the patch repair was examined from within the left hemithorax and from the abdominal aspect of the repair.

Histologic examination

The hiatal region and the esophagogastric junction were removed en bloc. Sections were taken for histologic evaluation from the region of the patch–esophagus interface and from the patch–diaphragm interface. The blocks were stained with hematoxylin and eosin and examined under light microscopy. The connective tissue capsule surrounding the prosthesis was characterized 3 and 28 weeks after implantation. Changes to the prosthesis were documented. Von Kossa and Alizarin S stains were used to confirm the presence of calcification within the prostheses. Specimens that had evidence of suppuration underwent Gram staining for identification of microorganisms.

Table 1 Adhesion scores [4]

Adhesion description	Score
None	0
Filmy, transparent, avascular	1
Opaque, translucent, avascular	2
Opaque, capillaries present	3
Opaque, larger vessels present	4

Table 2 Summary of postmortem findings

Repair	Interval (weeks)	Repair status	Grade of adhesions	Mesh erosion
Primary repair	3	Failed	3	N/A
Primary repair	3	Intact	4	N/A
Primary repair	28	Failed	3–4	N/A
Primary repair	28	Failed	3	N/A
Primary repair	28	Failed	3–4	N/A
Standard DualMesh	Perioperative death (day 2)	N/A	N/A	None
Standard DualMesh	Perioperative death (day 3)	Intact	N/A	None
Standard DualMesh	3	Intact	2	None
			3 to porous surface	
Standard DualMesh	28	Intact	1	None
Standard DualMesh	28	Intact	3	None
Standard DualMesh	28	Intact	1	None
			3 to porous surface	
Standard DualMesh	28	Failed	2	None
Large DualMesh	3	Intact	2	None
			3 to porous surface	
Large DualMesh	3	Intact	3	None
Large DualMesh	3 (death due intrathoracic intestinal volvulus)	Failed	N/A	None
Large DualMesh	28	Intact	2	None
Large DualMesh	28	Intact	2	None
Large DualMesh	28	Failed	3–4	None

N/A, not applicable

Results

Hiatal defects were created and repaired in 18 models. There were no intraoperative complications or deaths. Three postoperative deaths occurred. Two of these involved animals that had undergone a standard-sized prosthetic repair and died early in the postoperative period. One died 2 days postoperatively as a result of intraabdominal small bowel volvulus. The hiatal repair was intact. The second animal died 3 days postoperatively. The carcass was destroyed inadvertently and was unavailable for postmortem study.

The third death was that of an animal 25 days after repair using a large prosthesis. There had been failure of the prosthetic repair resulting in intrathoracic small bowel volvulus and strangulation. The sutures anchoring the anterior portion of the prosthesis to the remnant of the left crural pillar had pulled through the muscular fibers. Five animals in each group were available for postmortem and histologic examination. The postmortem results are summarized in Table 2.

Primary suture repair

Thoracotomy showed repair failure in four of the five models undergoing primary suture repair. In all models, the suture material was intact but had pulled through the diaphragmatic muscle. Laparotomy showed dense high-grade adhesions (grades 3 to 4) to all suture repairs.

Prosthetic repairs

Thoracotomy showed repair failure in 2 of 10 prosthetic repair models. In one animal undergoing repair with a standard-sized prosthesis, a knuckle of small bowel had herniated between the esophagus and prosthesis. In one animal undergoing repair with a large prosthesis, there was a major disruption of the repair, resulting in a large hernia sac containing numerous loops of small bowel. In two animals undergoing hiatal repair with a standard prosthesis, filmy peritoneal leaves were identified at the site of the prosthesis–esophagus interface. These formed a "sac." However, the leaves of the sac were adherent to one another and contained no viscera. They were filmy in contrast to the thicker hernia sacs containing viscera in the models with a failed repair. In those models in which the lung had been mobilized by division of the inferior pulmonary ligament, a robust band adhesion was identified between the lung and the prosthesis.

There was no evidence of adhesion or erosion of the prosthesis into the esophageal wall. In all DualMesh models, the esophagus moved freely over the cut edge of

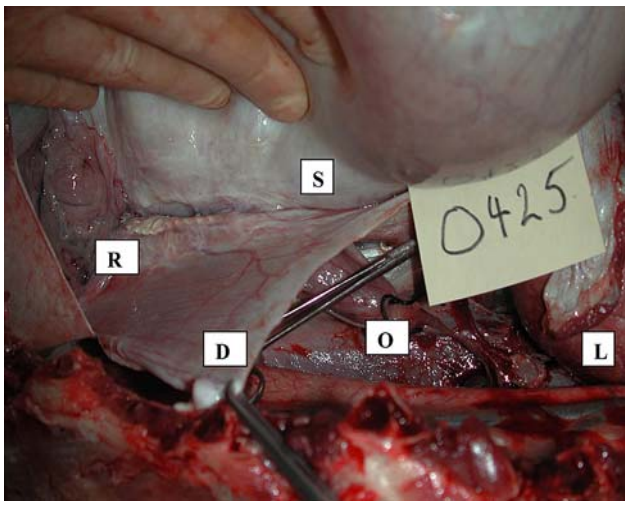


Fig. 2 The stomach (S) is retracted to demonstrate a prosthetic repair. Note the smooth capsule overlying the prosthesis and the paucity of adhesions. D, diaphragm; L, lung; O, esophagus; R, repair

the prosthesis. When examined from the abdominal aspect, the edge of the prosthesis was found to be encapsulated and distinct from the esophageal wall. At 3 weeks, the prostheses were incompletely encapsulated, and a clear margin of advancing encapsulation was noted on the abdominal surface of the prosthesis. By 28 weeks, all prostheses were completely encapsulated. In the majority of prosthesis models, there were filmy adhesions (grade 1 to 2) between the stomach and smooth surface of the DualMesh, which were broken down with gentle digital traction (Fig. 2).

In three models, more dense adhesions (grade 3) were noted at the site of folding of the prosthesis margin where its porous aspect came into contact with the underlying viscera. In four models that had significant adhesions between the viscera and diaphragm, the adhesions between the viscera and the prosthesis were less robust than between the viscera and the diaphragm. Three models had robust vascular adhesions (grades 3 to 4) between the underlying viscera and the abdominal aspect of the prosthesis. There was no evidence of prosthesis infection in any of the models.

Histologic evaluation of DualMesh patch

At 3 weeks, each prosthetic patch was incompletely surrounded by a capsule characterized by active vascular and fibroblastic proliferation, which was thicker overlying the porous aspect of the prosthesis. There was cellular and collagenous ingrowth between the interstices of the prosthesis to a depth up to one-fourth of its total thickness (Fig. 3). Particles of the prosthesis had separated and lay within the capsule surrounded by foreign body giant cells. In no specimen was a definite layer of mesothelial cells overlying the visceral aspect of the prosthesis identified. In one model,

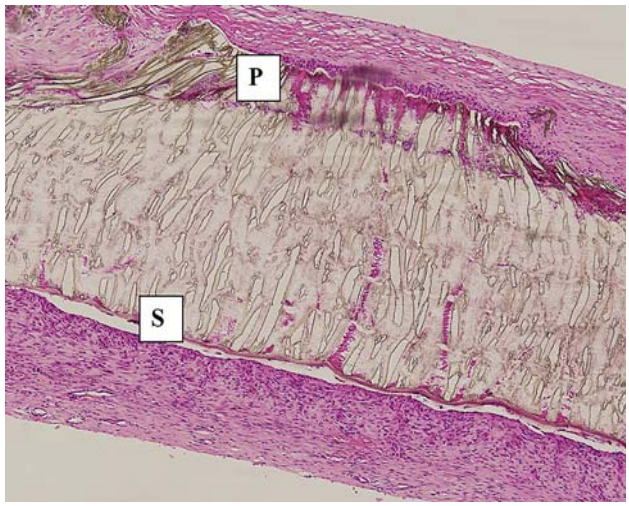


Fig. 3 Prosthesis capsule at 3 weeks. The capsule overlying the smooth surface of the graft consists of cellular and prominently vascularized fibrous tissue. S, smooth aspect of graft; P, porous aspect of graft

there were micro-abscesses at the interface between the prosthesis and the esophagus and between the prosthesis and the diaphragm. Gram staining failed to show bacteria. The mesh appeared to be undergoing degeneration.

At 28 weeks, the capsule had become less vascular, and the active inflammatory response was reduced (Fig. 4). There was a less prominent cellular infiltrate than at 3 weeks, but there still was ongoing extravasation of erythrocytes and deposition of hemosiderin in some specimens. The capsule over the porous side of the prosthesis was consistently thicker, and ingrowth had reached approximately halfway through its total thickness. Fragmentation of the porous aspect of the prosthesis appeared to be more advanced than at 3 weeks. There was greater separation of the fragments, and a florid foreign body giant cell reaction persisted. Over the nonporous aspect of the prosthesis, the capsule was thinner

Fig. 4 Prosthesis capsule at 28 weeks. At 28 weeks, the capsule consists of mature fibrous tissue, which is much thicker over the porous aspect. F, fragment; P, porous aspect; S, smooth aspect

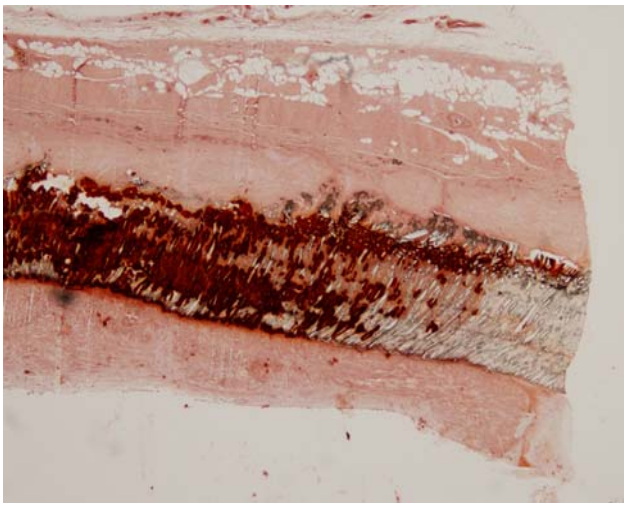


Fig. 5 Graft calcification at 28 weeks. Alizarin S stain is used to demonstrate graft calcification

and less cellular and appeared more organized than over the porous aspect of the mesh. Again, it was not possible to identify a defined mesothelial layer over the capsule.

There was evidence of calcification within all the prostheses. This was confirmed by staining with Von Kossa and Alazarin S stains and particularly prominent at the periphery of the prostheses (Fig. 5).

One specimen in which the repair had failed showed evidence of suppuration. This was characterized by an acute on chronic inflammatory response, with both neutrophils and mononuclear cells present. There were associated degenerative changes to the prosthesis. However, no bacteria were identified with Gram staining.

In one specimen, high-grade adhesions were noted macroscopically, and these were characterized histologically. Close to the prosthesis, the adhesions were vascular, with plump mesothelial cells. However, further away from the prosthesis, the adhesions appeared mature, with flattened mesothelial cells and less evidence of ongoing active inflammation.

Discussion

The long-standing perception among the surgical community that primary repair of large hiatal defects is associated with a high failure rate has resulted in the use of a number of graft materials. In the first half of the past century, autologous fascia lata [5] was used in an attempt to prevent recurrence. Later, prosthetic materials such as tantalum [6], polyvinyl formaldehyde sponge (Ivalon) [7], and nonexpanded polytetrafluoroethylene (Teflon) [8] were used. More recently, materials such as polypropylene, ePTFE, polyester, small intestine submucosa, and a variety of composite meshes have become available. Currently, one of the most influential studies on the use of mesh repair is a prospective randomized controlled trial by Frantzides et al. [2], in which patients with large hiatal defects were randomized to primary hiatal closure or primary closure with DualMesh. During a follow-up period of 3.3 years, recurrence rates in the DualMesh group (0%) were significantly less than in the primary closure group (22%).

However, the use of mesh at the hiatus may result in the additional risk of adhesion formation, which could potentially lead to failure of the repair. Hernia recurrence therefore remains the main problem after repair of large hiatal defects. Although the use of mesh has been shown to reduce recurrences, other concerns have been raised due to the occurrence of mesh erosion. A few studies have described the occurrence of intraluminal mesh erosion in the context of diaphragmatic repair, including one investigating polypropylene [9], PTFE [10], and ePTFE [11]. It is likely that this potential serious complication occurs more often than reported, and its impact on clinical outcome is therefore difficult to assess.

In a recent review by Granderath et al. [12], 38 published series containing 986 patients who had undergone mesh hiatal repair were identified. Although mesh erosion was not reported, routine endoscopic follow-up evaluation in the medium or long term was not performed in these studies. Therefore, no conclusions can be drawn regarding the risk of asymptomatic or mildly symptomatic erosion.

The properties of an ideal mesh, identified initially by Cumberland [13] and Scales [14], include chemical inertness, no associated inflammatory reaction, mechanical integrity, sterilizability, lack of physical modification by receptor tissues, lack of carcinogenicity, and convenient format for clinical use. Experimental evaluation of synthetic fascial prostheses usually involves application of one or more of the following end points: tissue integration and inflammation, adhesion and fistula formation, strength of repair, and infection and seroma formation.

In a review of experimental data, Morris-Stiff and Hughes [15] concluded that polypropylene and polyester meshes were better incorporated into host tissues than ePTFE, but more likely to result in adhesion formation. DualMesh, the most recently introduced ePTFE prothesis, is an asymmetric patch with one porous surface (approximately 60 μm) punched in a perimeteral pattern with one smooth nonporous surface.

Of the ePTFE patches, DualMesh is most frequently used for intraperitoneal repair of fascial defects. The porous aspect of the prosthesis is placed against the fascial defect, with the aim of more rapid host tissue incorporation, and the nonporous surface abuts the viscera. It is assumed that a smooth nonporous surface is less likely to form adhesions and subsequently erode into the abdominal viscera. A number of animal studies have supported

intraperitoneal use of ePTFE by demonstrating minimal visceral adhesions and encapsulation of the prosthesis [3, 16, 17].

However, none of the aforementioned experimental studies have addressed the specific clinical question concerning the behavior of a fascial graft positioned against the esophagus in a hiatal defect. In our study, a tension-free repair was performed with the DualMesh graft bridging the defect and with no crural closure performed. The cut edge of the graft was adjacent to the esophagus at about 180°, similar to the repair of large defects in clinical practice.

In our study, the most significant postmortem finding was the absence of adhesions or erosion of DualMesh into the esophagus. In all cases, the esophagus moved freely over the prosthesis edge. All grafts had become encapsulated at 28 weeks, and the majority had filmy adhesions only to the visceral aspect. The adhesions associated with the primary closure models were denser than those associated with the prosthetic repair. This may be due to the fact that coagulation diathermy was used to create the defects, with resulting local inflammatory changes.

In three models, more severe adhesions (grades 3 to 4) were encountered at the site where the porous aspect of the prosthesis came into contact with the underlying viscera. This finding occurred irrespective of mesh size (standard or large), suggesting that accurate positioning of the mesh in relation to the esophagus and other intraabdominal viscera is mandatory.

In our opinion, securing the mesh with sutures rather than with screws alone contributes to adequate fixation of the prosthetic repair. This clinical implication is supported by a recent study by Harrell et al. [18], who noted that DualMesh resulted in minimal adhesions in a model simulating laparoscopic ventral hernia repair, but who also found that DualMesh resulted in more shrinkage than other mesh types. The authors therefore clearly emphasized that adequate overlap of the mesh is a necessity for hernia repair.

At a microscopic level, our findings were in keeping for the most part with those of other authors. Our observations vary with others with regard to a number of potentially key factors however. First, encapsulation, although complete, did not take the form of true reepithelialization, but rather that of an acellular layer, which was easily disrupted [16]. Second, we noted degenerative changes, including fragmentation and calcification. Calcification has been noted by Kimber et al. [19], but not by other authors to our knowledge. Although the clinical implications of his finding are unclear, it can be speculated that calcification leads to increased rigidity of the prosthesis at the hiatus and therefore may result in dysphagia in the long term.

The use of mesh for repair of large hiatal defects has increased in recent years. The range of available biomaterials is increasing and their virtues extolled enthusiastically by manufacturers. Although DualMesh does not satisfy all the criteria of an ideal mesh, its widespread clinical use seems to reflect surgeons' acceptance. Before the widespread acceptance of any prosthesis as an adjunct for hiatal repair, however, a comprehensive evaluation should be undertaken with an animal model and then with well-designed clinical trials. This study, we believe, contributes to that process. The clinical implications of our study and previous experimental data are that folding and shrinkage of the mesh as a result of inflammatory reactions may lead to adhesions and subsequent failure of the repair. Therefore, adequate overlap and permanent fixation are of utmost importance. DualMesh is a commonly used biomaterial that has not been evaluated to date in an animal model of hiatal repair. The absence of adhesions and intraluminal erosion in our study may provide reassurance to surgeons using mesh at the hiatus.

Acknowledgments The study presented in this article was supported by research grants from the section of upper GI and HPB surgery at the Royal Australasian College of Surgeons and from W. L. Gore and Associates. This work is dedicated to the memory of Professor Christopher J. Martin, an inspirational esophageal surgeon and scientist.

References

1. Soyer T, Lempinen M, Cooper P (1972) A new venous prosthesis. Surgery 72:864–872
2. Frantzides C, Madan A, Carlson M, Stavropoulos G (2002) A prospective, randomized trial of laparoscopic polytetrafluoroethylene (PTFE) patch repair vs simple cruroplasty for large hiatal hernia. Arch Surg 137:649–652
3. Cristoforoni PM, Kim YB, Preys Z, Lay RY, Montz FJ (1996) Adhesion formation after incisional hernia repair: a randomized porcine trial. Am Surg 62:935–938
4. Boyers S, Diamond M, DeCherney A (1988) Reduction of postoperative pelvic adhesions in the rabbit with Gore-Tex surgical membrane. Fertil Steril 49:1066–1070
5. Hedblom C (1931) Diaphragmatic hernia: practice of surgery. Lewis Publishing Company; London, UK
6. Fusco EM (1960) The repair of hiatus hernia with tantalum mesh. Milita Med 125:189
7. Friedman MH, Mackenzie WC (1961) The clinical use of polyvinyl sponge Ivalon in the repair of esophageal hiatus hernia. Can J Surg 4:176–182
8. Merendino KA, Dillard DH (1965) Permanent fixation by Teflon mesh of the size of the esophageal diaphragmatic aperture in hiatus hernioplasty. Am J Surg 110:416–420
9. Carlson MA, Condon RE, Ludwig KA, Schulte WJ (1998) Management of intrathoracic stomach with polypropylene mesh prosthesis reinforced transabdominal hiatus hernia repair. J Am Coll Surg 187:227–230
10. Dutta S (2007) Prosthetic esophageal erosion after mesh hiatoplasty in a child, removed by transabdominal endogastric surgery. J Pediatr Surg 42:252–256
11. Coluccio G, Ponzio S, Ambu V, Tramontano R, Cuomo G (2000) Dislocation into the cardial lumen of a PTFE prosthesis used in the treatment of voluminous hiatal sliding hernia: a case report. Minerva Chir 55:341–345

12. Granderath F, Carlson M, Champion JK, Szold A, Basso N, Pointner R, Frantzides C (2006) Prosthetic closure of the esophageal hiatus in large hiatal hernia repair and laparoscopic antireflux surgery. Surg. Endosc 20:367–379
13. Cumberland VH (1952) A preliminary report on the use of a prefabricated nylon weave in the repair of ventral hernia. Med J Aust 1:143–144
14. Scales JT (1953) Tissue reactions to synthetic materials. Proc Royal Soc Med 46:647–652
15. Morris-Stiff GJ, Hughes LE (1998) The outcomes of nonabsorbable mesh placed within the abdominal cavity: literature review and clinical experience. J Am Coll Surg 186:352–367
16. Bellon JM, Contreras LA, Bujan J, Carrea-San Martin A (1996) Experimental assay of a DualMesh polytetrafluoroethylene prosthesis (nonporous on one side) in the repair of abdominal wall defects. Biomaterials 17:2367–2372
17. Bellon JM, Bujan J, Contreras LA, Jurado F (1997) Use of nonporous polytetrafluoroethylene prosthesis in combination with polypropylene prosthetic abdominal wall implants in prevention of peritoneal adhesions. J Biomed Mater Res 38:197–202
18. Harrell AG, Novitsky YW, Peindl RD, Cobb WS, Austin CE, Cristiano JA, Norton JH, Kercher KW, Heniford BT (2006) Prospective evaluation of adhesion formation and shrinkage of intraabdominal prosthetics in a rabbit model. Am Surg 72:808–813; discussion 813–814
19. Kimber CP, Dunkley MP, Haddock G, Robertson L, Carey FA, Cuschieri A (2000) Patch incorporation in diaphragmatic hernia. J Pediatr Surg 35:120–123

The Royal College of Surgeons of England

doi 10.1308/003588407X202182

Tom Dehn, Series Editor
E: thomas.dehn@rbbh-tr.nhs.uk

controversial topics in surgery

Mesh repairs in hiatal surgery

Hiatal hernia repair is noted to have a considerable failure rate. Using clips placed on the crural repair and on the fundoplication limbs we have noted a 20% failure rate 6 months following standard laparoscopic fundoplication – albeit the anatomical failure rate has a low correlation with symptomatic failure. Hashemi *et al.* (*J Am Coll Surg* 2000; **190**: 553–61) radiologically demonstrated a 29% recurrence rate (42% in those repaired laparoscopically) in type III hiatal hernia. Ketly and Falk oppose the wide-spread use of mesh hiatoplasty citing complications such as fibrotic stenosis and mesh erosion into the oesophagus, sometimes necessitating oesophagectomy. They compare the success of mesh hiatoplasty with that of mesh repair of parastomal hernia. Smith argues in favour of mesh repair on account of the tension of sutured hiatoplasty on the thin, attenuated and widened crural pillars observed in large hiatal defects. With increasing use of the more biologically compatible meshes now available, this technique will gain in popularity in an attempt to reduce the anatomical recurrence rate of sutured hiatoplasty.

Tom Dehn
Consultant Surgeon
E: thomas.dehn@rbbh-tr.nhs.uk

The case against mesh repairs in hiatal surgery

CLIVE J KELTY[1], GREGORY L FALK[1,2]

[1]Department of Upper GI Surgery, Concord Repatriation General Hospital, Concord, Sydney, New South Wales, Australia
[2]Department of Surgery, University of Sydney, New South Wales, Australia

CORRESPONDENCE TO:
Clive J Kelty, Department of Upper GI Surgery, Concord Repatriation General Hospital, Hospital Road, Concord, Sydney, NSW 2139, Australia
T: +61 2 9767 5000; F: +61 2 9745 1299; E: clive.kelty@bigfoot.com

Repair of hiatus hernias has evolved over recent years, and is now almost universally performed by the laparoscopic approach. There has been an increasing vogue for using prosthetic material to reinforce the repair in large hiatus hernia, particularly since the recurrence rate following this type of surgery is high, and recurrent hiatal herniation accounts for up to 70% of re-operations for failed antireflux surgery.[1,2] There is, however, a lack of hard data to back up this practice, and the use of prosthesis remains developmental.

The rationale for using prosthetic reinforcement

An enlarged hiatus is traditionally closed with interrupted large-gauge sutures (primary closure; simple cruroplasty).[3,4] However, any closure method is prone to disruption since the diaphragm is under repetitive stress due to the mechanics of respiration. The driving force for the use of prosthetic mesh placement is the reported recurrence rate in large hiatus hernia in the range of 5–30%.[1,2] It is widely recognised that the closure of large fascial defects elsewhere in the body (*e.g.* inguinal or ventral hernia) under similar mechanical stresses has been performed using prosthetic patches with excellent results.[5] However, the use of mesh is associated with an intense scarring response; although this is, in part, the rationale for its use, it can also cause problems, particularly when the site where it is used is considered.

The techniques used for hiatal repair vary in the studies reported, with some using primary closure of the crura followed by prosthetic onlay, whereas others are encircling the entire hiatus with a 'slit' cut in the mesh for the oesophagus (similar to an inguinal hernia repair).[6] It is presumed the mesh in this situation functions as a buttress, protecting the cruroplasty sutures from the intra-abdominal forces. A laparoscopic hiatus hernia 'tension-free' repair with prosthetic has been described, in which the defect is left open

and the prosthetic bridges the gap. This has also been modified using a relaxing incision in the diaphragm to the right of the hiatus, which is patched following repair of the crura. The theoretical advantages and disadvantages of the above procedures may be argued, but there is no evidence to demonstrate the superiority of any of these techniques.

Complications of prosthetic material

Various complications have been reported with the use of prosthetic material following hiatal hernia repair. These include inflammation, stricturing, bleeding and visceral erosion of the prosthesis. The most significant of these is erosion of the prosthetic material into the oesophagus, as well as complications related to severe adhesions and fibrotic strictures. This can be dependent upon the type of prosthetic material used; indeed, polypropylene mesh has been recognised as being responsible for erosion into hollow viscera when placed elsewhere within the body.[7] Teflon pledgets, despite supposedly being biologically inert, have been shown to erode into the oesophagus and stomach after fundoplication, requiring re-operation.[8,9] It has, therefore, been argued that more inert substances are more appropriate, including PTFE and newer 'biomaterials' (*e.g.* porcine acellular tissue graft, Surgisis®; Cook Biotech Inc., West Lafayette, IN, USA). Nylon meshes have been reported as eroding into the oesophagus, necessitating re-operation and, almost invariably, resection of the effected segment, requiring oesophagectomy.[6,9,10]

Although these reports could be dismissed as being anecdotal, there are further negative experiences associated with another prosthetic implant – namely the silastic Angelchik prosthesis which was used at the hiatus for the treatment of reflux disease.[11] This was associated with a large complication rate, and had to be removed in almost half of the patients in whom it was inserted. Its most dangerous complication was visceral erosion, and it caused bowel obstruction after extrusion into the lumen of the stomach, or was passed per rectum. It would seem that placement of any type of mesh prosthesis against a hollow organ is much more likely to cause complications than in incisional or inguinal hernia repair.

Discussion

The decision as to the advisability of a mesh repair hinges upon the rate of recurrence and complications in the longer term, compared with the recurrence rate and complications of primary repair alone. In the literature, an improvement is noted in the results of incisional and inguinal hernia repair as prosthetic utilisation became more common; thus, the extension of prosthetic use to include the large hernia of the oesophageal hiatus initially seems logical. However, the presence of a hollow organ changes the paradigm. A better analogy may be that of repair of parastomal hernia, which is associated with high rates of morbidity, mortality and recurrence (in up to two-thirds of patients having simple fascial repair). However, mesh repair is still associated with a recurrence rate of up to 40%,[12] and re-operation for complications is frequent (25–30%) – similar to those reported in hiatal hernia surgery.

It could be argued that since recurrence occurs in approximately 10–30% of patients who undergo primary repair of large hiatus hernias without prosthetic mesh, the use of mesh placement at the hiatus of every large defect to reduce the likelihood of recurrence would not be necessary in 70–90% of patients. These patients are thus put at risk of mesh-related complications unnecessarily. However, the data required (and lacking presently) are the complication rates from repair of hernias with and without mesh, over a long period of time. Of the studies performed to date, there is rarely long-term follow-up (the mean follow-up is at best 5 years). The majority of symptomatic problems will occur after this period of time; indeed, erosion of prosthetic material into the oesophagus has been reported over 9 years following the original surgery.[9] More importantly, it is the impact upon quality of life that treatment of the complications incurs that may be the deciding factor. Even assuming a low rate of complications of mesh repair, the morbidity and mortality associated with oesophagectomy (even in the best hands) is significant, and we would argue has a far greater impact on quality of life for these patients than a laparoscopic revision of hiatus hernia repair. This may be compounded by the elderly nature of this population at the time of primary surgery, who may be 10 or 15 years older at the time of revision and unable to tolerate revisional surgery.

We would argue that whilst there have been some promising early results with the use of prosthetic material, the long-term outcomes remain unknown. It may be that, when long-term data are available, we will find that the implications of complications are much higher than currently thought. Albeit the risk of prosthesis-related complications appears to be infrequent (ranging from 2–20%[6]), when one considers the potential need for major radical surgery in the event of complications, this is not a valid reason for performing routine mesh placement in the repair of hiatus hernias, and cannot justify the wide-spread adoption of what remains an unproven technique. A more appropriate policy, therefore, may be to consider mesh hiatoplasty in the select group of patients who have a recurrence following primary repair as the risk of complications can be better justified.

References

1. Smith GS, Isaacson JR, Draganic BD, Baladas HG, Falk GL. Symptomatic and radiological follow-up after para-esophageal hernia repair. *Dis Esophagus* 2004; **17**: 279–84.
2. Stein HJ, Feussner H, Siewert JR. Failure of antireflux surgery: causes and manage-

ment strategies. *Am J Surg* 1996; **171**: 36–40.

3. Hinder RA, Klingler PJ, Perdikis G, Smith SL. Management of the failed antireflux operation. *Surg Clin North Am* 1997; **77**: 1083–98.
4. Gantert WA, Patti MG, Arcerito M, Feo C, Stewart L, DePinto M *et al*. Laparoscopic repair of paraesophageal hiatal hernias. *J Am Coll Surg* 1998; **186**: 428–33.
5. Lichtenstein IL, Amid PK, Shulman AG. The tension-free repair of groin hernias. In: Nyhus LM, Condon RE. (eds) *Hernia*. Philadelphia, PA: Lippincott, 1995; 237–47.
6. Granderath FA, Carlson MA, Champion K, Szold A, Basso N, Pointer R *et al*. Prosthetic closure of the esophageal hiatus in large hiatal hernia repair and laparoscopic antireflux surgery. *Surg Endosc* 2006; **20**: 367–79.
7. Gillion JF, Begin GF, Marecos C, Fourtanier G. Expanded polytetrafluoroethylene patches used in the intraperitoneal or extraperitoneal position for repair of incisional hernias of the anterolateral abdominal wall. *Am J Surg* 1997; **174**: 16–9.
8. Dally E, Falk GL. Teflon pledget reinforced fundoplication causes symptomatic gastric and esophageal lumenal penetration. *Am J Surg* 2004; **187**: 226–9.
9. Arendt T, Stuber E, Monig H, Folsch UR, Katsoulis S. Dysphagia due to transmural migration of surgical material into the esophagus nine years after Nissen fundoplication. *Gastrointest Endosc* 2000; **51**: 607–10.
10. Trus TL, Bax T, Richardson WS, Branum GD, Mauren SJ, Swanstrom LL *et al*. Complications of laparoscopic paraesophageal hernia repair. *J Gastrointest Dis* 1997; **1**: 221–8.
11. Crookes PF, DeMeester TR. The Angelchik prosthesis: what have we learned in fifteen years? *Ann Thorac Surg* 1994; **57**: 1385–6.
12. Geisler DJ, Reilly JC, Vaughan SG, Glennon EJ, Kondylis PD. Safety and outcome of use of nonabsorbable mesh for repair of fascial defects in the presence of open bowel. *Dis Colon Rectum* 2003; **46**: 1118–23

Elucidation of the causes of dyspnoea in the presence of giant hiatus hernia

Reference:

1. Falk GL, Little SC. Mechanisms of dyspnoea in giant hiatus hernia: an indication to perform surgery? European Surgery. 2018;50(4):167-8.

2. Naoum C, Kritharides L, Falk GL, Martin D, Yiannikas J. Left atrial compression and right ventricular outflow tract diameter on echocardiography are independently associated with exercise capacity in patients with large hiatal hernia. Echocardiography. 2018;35(5):592-602.

3. Naoum C, Kritharides L, Ing A, Falk GL, Yiannikas J. Changes in lung volumes and gas trapping in patients with large hiatal hernia. The Clinical Respiratory Journal. 2017;11(2):139-50.

4. Naoum C, Kritharides L, Gnanenthiran SR, Martin D, Falk GL, Yiannikas J. Valsalva maneuver exacerbates left atrial compression in patients with large hiatal hernia. Echocardiography. 2017;34(9):1305-14.

5. Naoum C, Puranik R, Falk GL, Yiannikas J, Kritharides L. Postprandial left atrial filling is impaired in patients with large hiatal hernia and improves following surgical repair. Int J Cardiol. 2015;182:291-3.

6. Naoum C, Falk G, Yiannikas J. Exercise-induced left atrial compression by a hiatus hernia. J Am Coll Cardiol. 2011;58(14):e27.

7. Naoum C, Falk GL, Ng AC, Lu T, Ridley L, Ing AJ, et al. Left atrial compression and the mechanism of exercise impairment in patients with a large hiatal hernia. J Am Coll Cardiol. 2011;58(15):1624-34.

8. Zhu JC, Becerril G, Marasovic K, Ing AJ, Falk GL. Laparoscopic repair of large hiatal hernia: impact on dyspnoea. Surg Endosc. 2011;25(11):3620-6.

short communication

Eur Surg (2018) 50:167–168
https://doi.org/10.1007/s10353-018-0531-3

european surgery
ACA Acta Chirurgica Austriaca

Mechanisms of dyspnoea in giant hiatus hernia: an indication to perform surgery?

Gregory Leighton Falk · Sophia C. Little

Received: 24 January 2018 / Accepted: 10 April 2018 / Published online: 25 April 2018

Summary
Background The physiology of dyspnoea associated with giant hiatus hernia has not been well understood; however, it is generally considered a contraindication for surgery.
Methods Recent studies into mechanisms and prevalence of dyspnoea are discussed.
Results Recent studies suggest that dyspnoea is present in 80% of cases of massive hiatus hernia. Cardiac compression from massive hiatus hernia is a known contributor to dyspnoea in this patient group, as well as pulmonary aspiration.
Conclusions Paradoxically, dyspnoea could be considered as an indication for surgery in patients presenting with giant hiatus hernia, once the mechanism is established.
Novel points Dyspnoea in the presence of a substantially large hiatus hernia has long been considered unrelated and a contraindication to surgery. We present the results of varied studies that suggest dyspnoea, when the mechanism is established, is in fact an indication for surgery in giant hiatus hernia.

Keywords Cardiac function testing · Dyspnoea · Herniorrhaphy · Hiatus hernia · Surgery contraindications

G. L. Falk, MBBS FRACS FRCS (✉) · S. C. Little, B. AVBS (Hons)
Sydney Heartburn Clinic, Suite 29, 12–18 Tryon Rd, NSW 2070 Lindfield, Australia
sydney.heartburn@gmail.com

G. L. Falk, MBBS FRACS FRCS
Repatriation General Hospital Concord, NSW 2137 Concord, Australia

Dyspnoea in patients with giant hiatus hernia (Fig. 1) is not well recognised amongst the general medical community. Heartburn and regurgitation are not necessarily a phenomenon of giant hiatus hernia; however, dysphagia, early satiety and post-prandial chest pain are often present in the subacute situation. Common symptoms of giant hiatus hernia include dyspnoea (83%), regurgitation (57%), heartburn (60%), dysphagia (53%) and early satiety (80%) and non-cardiac chest pain (80%) [1].

Recently, dyspnoea has featured in up to 80% of cases [1–3]. Dyspnoea, however, has always been considered a risk factor for surgery, and may prevent necessary surgery. Following surgery, dyspnoea has improved, as has lung function [1, 2, 4]. However, changes observed in respiratory function were minimal and did not appear to explain the substantial improvement in dyspnoea. Recent work performed in Sydney demonstrated changes in cardiac inflow, associated with the presence of the mediastinum mass of a large hiatus hernia [3]. Many patients have anomalies of cardiac return, with compression of the left atrium and inferior pulmonary veins identifiable by different modalities including echocardiogram, magnetic resonance imaging and cardiac CT [3, 5, 6]. Reliable demonstration of cardiac inflow obstruction by stress echocardiogram needs to be performed with an adequate ingested volume (full stomach) and using the technique established by Naoum and Yiannikas in their various publications.

Improvement in lung function studies following operation was significant but within the normal range, suggesting a lesser respiratory effect upon dyspnoea [7]. More recently, the senior author has demonstrated a high rate of pulmonary aspiration in 68% of 80 patients tested using scintigraphic reflux measures, which may further add to the sensation of dyspnoea

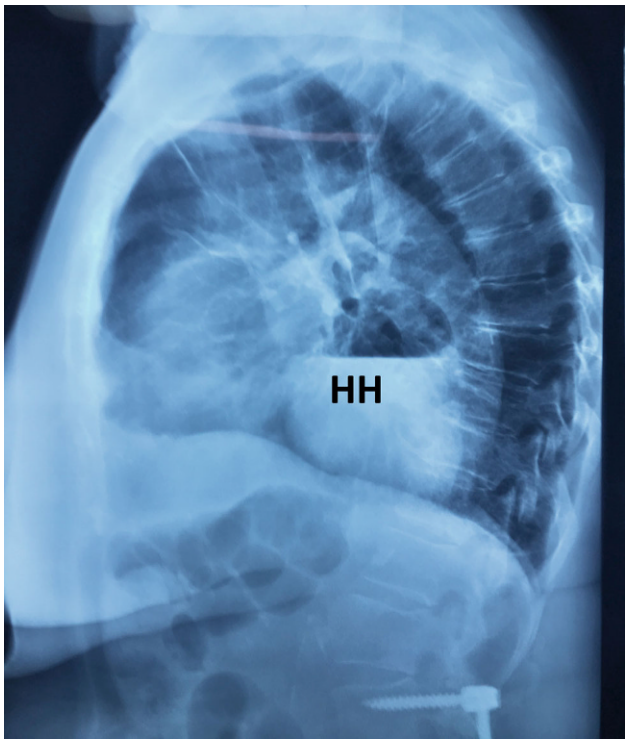


Fig. 1 Massive hiatus hernia on barium meal, profile view

[8]. Anaemia occurs in 30% and may exacerbate dyspnoea.

A large and symptomatic hiatus hernia has a risk for acute complications and mortality up to 14% at 4 years [3, 9]. As surgery can be performed safely and eliminate the risk of such complications over a reasonable period of time, it is relatively indicated [9]. Left atrial compression or inflow obstruction identified preoperatively predicts improvement in exercise tolerance and the symptom of dyspnoea, and quality of life [9, 10].

Dyspnoea is a surprisingly common symptom in large hiatus hernia and frequently reflects cardiac inflow obstruction caused by the mediastinal mass of stomach. It is an indication for surgery rather than a contraindication as previously thought, especially if there is demonstrable cardiorespiratory compression. Dyspnoea may now be added to the symptomatic evaluation of giant hiatus hernia reliably, and may well constitute an indication for surgery.

Acknowledgements We would like to thank co-workers Professor John Yiannikas and Dr Christopher Naoum, from the Department of Cardiology, Repatriation General Hospital Concord, NSW, Australia.

Conflict of interest G.L. Falk and S.C. Little declare that they have no competing interests.

References

1. Low DE, Simchuk EJ. Effect of paraesophageal hernia repair on pulmonary function. Ann Thorac Surg. 2002;74(2):333–7.
2. Zhu JC, Becerril G, Marasovic K, Ing AJ, Falk GL. Laparoscopic repair of large hiatal hernia: impact on dyspnoea. Surg Endosc. 2011;25(11):3620–6.
3. Naoum C, Falk GL, Ng ACC, et al. Left atrial compression and the mechanism of exercise impairment in patients with a large hiatal hernia. J Am Coll Cardiol. 2011;58(15):1624–34.
4. Carrott PW, Hong J, Kuppusamy M, Koehler RP, Low DE. Clinical ramifications of giant paraesophageal hernias are Underappreciated: making the case for routine surgical repair. Ann Thorac Surg. 2012;94(2):421.
5. Naoum C, Kritharides L, Thomas L, et al. Modulation of phasic left atrial function and left ventricular filling in patients with extrinsic left atrial compression by hiatal hernia. Int J Cardiol. 2014;176(3):1176–8.
6. Naoum C, Puranik R, Falk GL, Yiannikas J, Kritharides L. Postprandial left atrial filling is impaired in patients with large hiatal hernia and improves following surgical repair. Int J Cardiol. 2015;182:291–3.
7. Naoum C, Kritharides L, Ing A, Falk GL, Yiannikas J. Changes in lung volumes and gas trapping in patients with large hiatal hernia. Clin Respir J. 2017;11(2):139–50.
8. Mugino M, Little SC, Falk GL. Unpublished. 2018.
9. Le Page PA, Furtado R, Hayward M, et al. Durability of giant hiatus hernia repair in 455 patients over 20 years. Ann R Coll Surg Engl. 2015;97(3):188–93.
10. Gibson SC, Wong SC, Dixon AC, Falk GL. Laparoscopic repair of giant hiatus hernia: prosthesis is not required for successful outcome. Surg Endosc. 2013;27(2):618–23.

DOI: 10.1111/echo.13835

ORIGINAL INVESTIGATIONS

WILEY Echocardiography

Left atrial compression and right ventricular outflow tract diameter on echocardiography are independently associated with exercise capacity in patients with large hiatal hernia

Christopher Naoum MBBS, PhD[1] | Leonard Kritharides MBBS, PhD[1] | Gregory L. Falk MBBS[2] | David Martin MBBS[2] | John Yiannikas MBBS[1]

[1]Department of Cardiology, Concord Hospital, The University of Sydney, Sydney, NSW, Australia

[2]Department of Upper GI Surgery, Concord Hospital, The University of Sydney, Sydney, NSW, Australia

Correspondence
John Yiannikas, Department of Cardiology, Concord Hospital, The University of Sydney, Sydney, Concord NSW, Australia.
Email: john.yiannikas@sydney.edu.au

Introduction: Large hiatal hernia (HH) is often associated with left atrial (LA) compression, anteroposterior cardiac compression (manifesting as reduced right ventricular outflow tract (RVOT) diameter), and left ventricular (LV) compression (manifesting as systolic paradoxical outward motion (LV-PM) of the posterobasal LV segment). Exercise impairment, also common in this population, improves following HH surgery. We aimed to identify echocardiographic parameters independently associated with exercise impairment due to HH-mediated cardiogenic compression.

Methods: Patients with a large HH (>30% intra-thoracic stomach, n = 163) referred for cardiac evaluation were included. Echocardiographic parameters were retrospectively analyzed in relation to HH-related LA compression severity and the presence of LV-PM. Echocardiographic parameters independently associated with exercise capacity were identified by multivariable analysis.

Results: Mean baseline metabolic equivalents were reduced (70 ± 28% predicted). Moderate–severe LA compression and LV-PM were present in 91 of 163 (56%) and 65 of 162 (40%) patients, respectively. Patients with moderate–severe LA compression and LV-PM had decreased LA and LV dimensions. Moderate–severe LA compression was also associated with reduced RVOT diameter while LV-PM predicted a greater reduction in LV volumes. LA compression and RVOT diameter were independently associated with baseline exercise capacity and increased following HH surgery performed in a subgroup (n = 72, LA diameter: 14 ± 5 vs 20 ± 4 mm/m^2; RVOT diameter: 17 ± 3 vs 19 ± 3 mm/m^2, $P < .001$ for both). Conversely, LV-PM was not independently associated with exercise capacity.

Conclusion: Hiatal hernia-related cardiac compression reduces LA and RVOT dimensions. These parameters are independently associated with baseline exercise capacity and improve following HH surgery. LV-PM is associated with decreased LV volumes but not exercise capacity in this population.

KEYWORDS
exercise tolerance, hiatal hernia, left atrium, right ventricle

1 | INTRODUCTION

The detection of a hiatal hernia (HH) on echocardiography is often considered a benign condition.[1] However, large HH can be associated with left atrial (LA) compression and significant symptoms including dyspnea, chest pain, and syncope.[2–10] Despite a high prevalence of dyspnea and impaired exercise capacity in this population, the cause of these symptoms is frequently attributed to comorbidities. Reliable echocardiographic identification of those patients with dyspnea due to HH-mediated cardiogenic compression is important as it may facilitate the decision to undergo corrective surgery.

There have only been 2 small case series describing the echocardiographic characteristics of patients with HH. One reported on the features that distinguished extrinsic LA compression by a HH from an intrinsic LA mass.[11] A second series reported on LA compression in different imaging planes and during respiration, as well as the presence of paradoxical systolic motion of the posterobasal left ventricular (LV-PM) wall as a marker of significant extrinsic LV compression.[12] In both studies, quantitative two-dimensional or Doppler echocardiographic parameters and their relationship to exercise capacity were not reported.

We previously demonstrated improved LA diameter and reduced LA inflow velocities following corrective HH surgery and identified a correlation between the increase in LA diameter and the improvement in exercise capacity improvement following HH surgery.[13] However, the sample size in that study was small, and detailed echocardiographic analyses were lacking. In particular, changes to LA and LV filling, the impact of basal LV compression and changes to the right ventricular outflow tract (RVOT) were not evaluated. Most importantly, the association of these parameters with exercise capacity was not studied, and thus, their functional significance is unknown.

In this study, we report on the echocardiographic findings of a large consecutive cohort of patients with large HH, with particular emphasis on LA compression, paradoxical systolic motion of the posterobasal LV (LV-PM), and the RVOT. We investigate the echocardiographic measures of cardiac compression that are associated with exercise impairment in HH patients and the impact of corrective HH surgery.

2 | METHODS

Consecutive patients with a large HH (>30% intrathoracic stomach by endoscopic or barium swallow evaluation) who were being considered for surgery and referred to a cardiology outpatient clinic, or referred for cardiac evaluation and identified to have a large HH were considered for the present analysis. All patients underwent echocardiography using a prespecified protocol and, unless contraindicated, treadmill exercise testing. Two primary analyses were retrospectively performed. First, the association of echocardiographic parameters with the severity of HH-related LA compression and the presence or absence of LV-PM was investigated. Second, echocardiographic parameters associated with reduced exercise capacity were identified. In a subgroup, postoperative evaluation was performed and changes in echocardiographic parameters were quantified. The Sydney Local Health District Human Research Ethics Committee approved the study.

2.1 | Transthoracic echocardiography

Resting Doppler echocardiography was performed by an experienced cardiac sonographer using a Vivid-7 or Vivid-9 Dimension cardiac ultrasound (General Electric, Horten, Norway). Images were digitally recorded and batch analysis performed by a single observer. Patients were advised to consume a meal prior to presenting for clinical and echocardiographic evaluation.

2.2 | Echocardiographic parameters

The severity of LA compression was graded qualitatively (none, mild, moderate, severe) by visual assessment in parasternal and apical echocardiographic views (examples shown in Figure 1).[13] Posterobasal LV compression was identified by the presence of early systolic paradoxical outward motion of the posterobasal LV wall (LV-PM) adjacent to the HH as has been reported previously.[12] This was assessed in the parasternal long-axis and apical three-chamber views and is reported as being present or absent (Movies S1 and S2).

Left ventricular dimensions and fractional shortening were quantified according to American Society of Echocardiography guidelines,[14] and LV volumes and ejection fraction were measured using the Simpson's biplane method. As a measure of anteroposterior right ventricular compression, proximal right ventricular outflow tract (RVOT) diameter was measured in the parasternal short-axis view at end-diastole as described previously.[15] Maximal anteroposterior LA diameter was measured in the parasternal long-axis view between the midpoints of the anterior and posterior LA walls as described previously.[13] Pulse-wave Doppler assessment of the mitral valve inflow (early: E, and late: A, velocities and deceleration time: DT) was performed as previously described.[16] Peak systolic (S) and diastolic (D) pulse-wave Doppler velocities were measured at the LA inflow in a modified apical five-chamber view sampling LA inflow adjacent to the interatrial septum. Right ventricular systolic pressure (RVSP) was derived from the systolic RV to right atrial (RA) pressure gradient using the velocity of the tricuspid regurgitant envelope. RA pressure, assumed to be 5 mm Hg, was then added to the calculated gradient. Transmitral pulse-wave Doppler measurements were averaged over 3 cardiac cycles. For LA inflow velocities and RVSP measurements, the highest obtained values were recorded. Given the LA and RVOT diameters were key quantitative measures of cardiac compression in this cohort, repeated measurements were performed in 10% of randomly selected patients by the initial observer (CN) and a second independent observer (JY). Coefficients of variation and absolute differences in these measurements indicated an acceptable level of intra- and inter-observer reproducibility (Table S1).

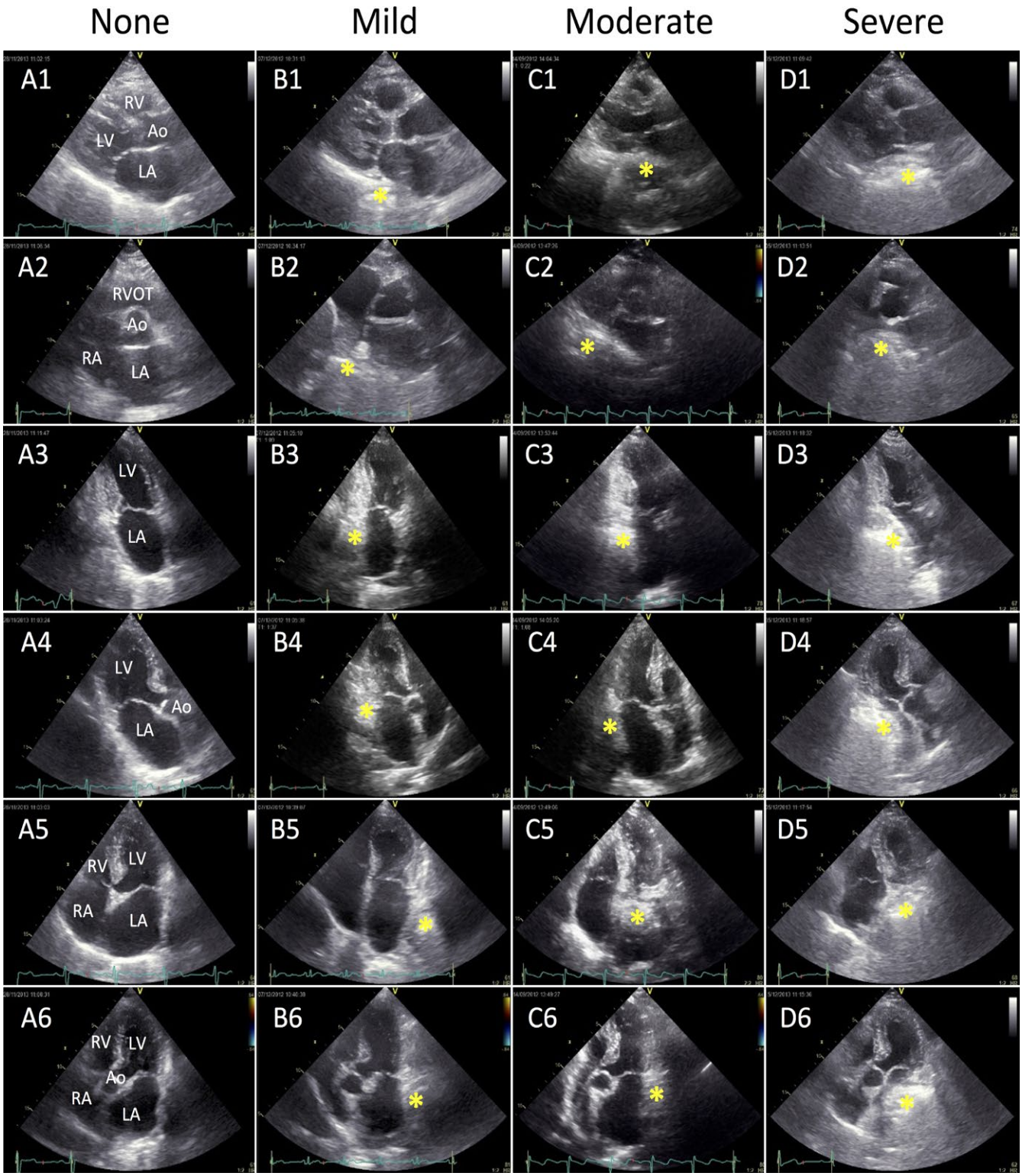


FIGURE 1 Left atrial compression by hiatal hernia on echocardiography. Echocardiographic views showing examples of increasing LA compression (none, A1–6; mild, B1–6; moderate, C1–6; severe, D1–6) by hiatal hernia (*). Parasternal (upper 2 rows) and apical (rows 3–6) views are demonstrated. Note the increasing deformation and decreasing LA chamber size with increasing grades of LA compression severity. In the patient with severe LA compression, obliteration of the LA by HH persists with tilting of the echo probe from the posterior apical four-chamber view to a more anterior imaging plane with the aortic root in view. LA = left atrium; RA = right atrium; LV = left ventricle; RV = right ventricle; RVOT = right ventricular outflow tract; Ao = aortic root

2.3 | Exercise capacity assessment

Symptom-limited maximal treadmill exercise was performed as part of the clinical evaluation using the Bruce protocol with a physician present to encourage maximal exercise. An initial zero gradient stage ("warm-up phase") was necessary in some elderly patients with compromised exercise capacity, and the test was most commonly discontinued due to dyspnea, fatigue, or peripheral muscle fatigue. Exercise duration was used to estimate absolute metabolic equivalents (METS) achieved, which is expressed as a percentage of age-predicted values.[17,18]

2.4 | Statistical analysis

Continuous data are expressed as mean ± SD and categorical data as frequencies (percentages). Doppler echocardiographic parameters are indexed to body surface area.

Patients were stratified into 2 groups according to baseline LA compression severity ("none–mild" or "moderate–severe") and according to the presence or absence of posterobasal LV-PM. Continuous echocardiographic parameters were then compared between these groups at baseline using an unpaired *t* test or Mann–Whitney test; and categorical variables using a chi-square test or chi-square test for trend, as appropriate. Changes in quantitative parameters following surgery were assessed using a paired *t* test or Wilcoxon signed-rank test, as appropriate.

Univariate clinical and echocardiographic parameters associated with exercise capacity (absolute METS achieved) were first identified using Spearman correlation. Multivariate linear regression was then used to identify independently associated echocardiographic parameters after correcting for age, body mass index (BMI), sex, and the number of cardiorespiratory comorbidities (aggregated into a single score). Given the purpose of the analysis was to understand the impact of HH-related cardiac compression on exercise capacity in this population, LA compression, LV-PM, and quantitative echocardiographic variables with a univariate $P \leq .10$ that changed significantly following surgery (and were therefore unique to the HH) were included by stepwise regression. In cases of collinearity ($R \geq 0.50$), the more significant univariate predictor (higher correlation coefficient) was included. Standardized beta (β) coefficients are reported for individual variables, and the adjusted R^2 for the overall model.

Statistical analyses were performed using Graph Pad Prism 6.0d (GraphPad Software, La Jolla, CA, USA) and IBM SPSS Statistics for Macintosh version 22 (IBM Corp., Armonk, NY, USA). A 2-tailed *P*-value <.05 was considered statistically significant.

3 | RESULTS

Between May 2009 and February 2014, 168 consecutive patients with large HH underwent cardiac evaluation and echocardiography. Five patients were excluded due to incomplete clinical data leaving 163 patients in the final cohort. Baseline clinical and echocardiographic characteristics are presented in Tables 1 and 2, respectively. The majority of patients reported symptoms consistent with New York Heart Association (NYHA) class II or III functional impairment, and baseline exercise capacity was reduced (METS achieved: 70 ± 28% predicted). Baseline LA and LV dimensions and LV volumes were at the lower end of age-appropriate normal values.[14] Mean LV diastolic mass was normal (males 80 ± 16 g/m^2, females 70 ± 14 g/m^2) but was increased (>102 g/m^2 for males, >88 g/m^2 for females[14]) in 15 patients (12 female). The mean LV ejection fraction was normal for the overall group (66 ± 8%) but was below 55% in 16 patients (range: 39%–54%). Left-sided valvular lesions considered to be moderate or severe by qualitative assessment were observed in 7 of 163 (4%) patients only.

TABLE 1 Baseline clinical characteristics

	N = 163
Demographics	
Age—y	70 ± 10
Female gender—n	122/163 (75)
Body mass index—kg/m^2	
Mean ± SD	30 ± 5
Median (IQR)	30 (27–33)
Systolic blood pressure—mm Hg	
Mean ± SD	138 ± 10
Median (IQR)	135 (130–145)
Symptoms and functional class[a]	
NYHA class	
I	37/160 (23)
II	61/160 (38)
III	58/160 (36)
IV	4/160 (3)
Postprandial dyspnea	78/163 (48)
Comorbidities	
Coronary artery disease	24/163 (15)
Percutaneous coronary intervention or coronary bypass grafting	14/163 (9)
Congestive heart failure	2/163 (1)
Atrial arrhythmia	11/163 (7)
Valvular heart disease[b]	7/163 (4)
Diabetes	21/163 (13)
Dyslipidemia	101/163 (62)
Hypertension	100/163 (61)
Previous smoker	48/163 (29)
Current smoker	0/163 (0)
Asthma	28/163 (17)
Chronic obstructive pulmonary disease	12/163 (7)
Pulmonary emboli	11/163 (7)
Sleep apnea	16/163 (10)
Other pulmonary disease	12/163 (7)
Exercise capacity	N = 153
Resting heart rate—bpm	76 ± 13
Peak heart rate—bpm	135 ± 20
Peak heart rate—% of maximum predicted heart rate[c]	90 ± 11
METS achieved	5.8 ± 2.6
METS achieved—% of predicted	70 ± 28

[a]NYHA class not assessable in 2 patients due to paraplegia and in 1 patient due to significant musculoskeletal disability. Exertional dyspnea not assessable in 1 patient due to paraplegia.
[b]Valvular heart disease defined as moderate or greater left-sided valvular regurgitation or stenosis on baseline echocardiography by qualitative assessment.
[c]Equals 220—patient age.

TABLE 2 Echocardiographic parameters stratified by LA compression and LVPM

Echocardiographic parameter	All patients[a] N = 163	None–mild LAC N = 72	Mod–severe LAC N = 91	*P*-value	LV-PM absent N = 97	LV-PM present N = 65	*P*-value
LA diameter index—mm/m^2	16 ± 5	20 ± 3	13 ± 4	<.001	17 ± 5	14 ± 5	.0002
LV diastolic diameter index—mm/m^2	22 ± 3	24 ± 4	21 ± 3	<.001	23 ± 3	22 ± 3	.007
LV systolic diameter index—mm/m^2	13 ± 3	14 ± 4	12 ± 3	<.001	13 ± 3	12 ± 3	.001
Average wall thickness index—mm/m^2	5.8 ± 1.1	5.7 ± 1.1	5.9 ± 1.1	.23	5.8 ± 1.1	6.0 ± 1.2	.26
Fractional shortening—%	44 ± 11	41 ± 11	45 ± 10	.03	42 ± 11	46 ± 11	.053
LV diastolic volume index—mL/m^2	34 ± 10	36 ± 10	33 ± 10	.01	36 ± 10	31 ± 9	.0002
LV systolic volume index—mL/m^2	12 ± 5	13 ± 6	11 ± 5	.18	12 ± 5	11 ± 5	.01
LV stroke volume index—mL/m^2	22 ± 6	24 ± 6	21 ± 6	.01	24 ± 6	20 ± 6	.0004
LV ejection fraction—%	66 ± 8	66 ± 9	65 ± 8	.46	66 ± 8	65 ± 9	.51
LV diastolic mass index—g/m^2	72 ± 15	74 ± 15	71 ± 16	.24	72 ± 15	72 ± 16	.82
Heart rate—bpm	76 ± 13	73 ± 11	78 ± 13	.01	74 ± 12	79 ± 12	.01
RVOT diameter index—mm/m^2	17 ± 3	18 ± 3	16 ± 3	<.0001	17 ± 3	17 ± 3	.26
Atrial inflow							
S-wave—cm/s	78 ± 20	71 ± 15	83 ± 22	.0003	75 ± 16	83 ± 24	.02
D-wave—cm/s	53 ± 16	51 ± 14	55 ± 17	.12	52 ± 15	55 ± 17	.71
S/D ratio	1.51 ± 0.40	1.46 ± 0.38	1.56 ± 0.41	.12	1.49 ± 0.38	1.54 ± 0.43	.55
Mitral valve inflow							
E-wave—cm/s	72 ± 16	72 ± 17	73 ± 17	.79	72 ± 15	72 ± 18	.94
A-wave—cm/s	86 ± 20	83 ± 20	87 ± 21	.31	84 ± 19	88 ± 22	.52
E/A ratio	0.87 ± 0.21	0.89 ± 0.24	0.85 ± 0.19	.59	0.88 ± 0.21	0.85 ± 0.22	.29
DT—ms	206 ± 46	203 ± 47	208 ± 45	.27	202 ± 50	212 ± 38	.02
RV systolic pressure—mm Hg	33 ± 8	33 ± 8	33 ± 8	.97	33 ± 8	33 ± 8	.76

[a]Echo parameters measurable in >95% patients except: S-wave (83%); D-wave (79%); E- and A-wave (91%); DT (90%); LVOT stroke volume and cardiac index (93%); RVSP (72%).

Seventy-two patients (72 of 163, 44%) underwent surgery and postoperative evaluation. Apart from higher systolic blood pressure in the group undergoing postsurgery review, there were no differences in clinical parameters between patients that did and did not undergo postoperative assessment (Table S2). However, baseline LA diameter was smaller and LV-PM more frequent in the group that underwent postoperative echocardiography (Table S3). Exercise capacity increased significantly following surgery (METS achieved: 72 ± 28% preop vs 101 ± 30% postop, $P < .001$).

3.1 | Qualitative LA compression and LVPM

Left atrial compression was graded none, mild, moderate, or severe in 19 of 163 (12%), 53 of 163 (33%), 50 of 163 (31%), and 41 of 163 (25%) patients, respectively. LV-PM was present in 65 of 162 (40%) patients and was not assessable in 1 patient due to prior posterobasal myocardial infarction. Increasing severity of LA compression was associated with a higher frequency of LV-PM (Figure 2).

3.2 | Relationship among LA compression, LVPM, and quantitative echocardiographic parameters

Echocardiographic parameters, stratified by the severity of LA compression and the presence of LV-PM, are described in Table 2. Compared to patients with none–mild LA compression, patients with moderate–severe LA compression had decreased LA, LV, and RVOT dimensions, decreased biplane LV diastolic volume (33 ± 10 mL/

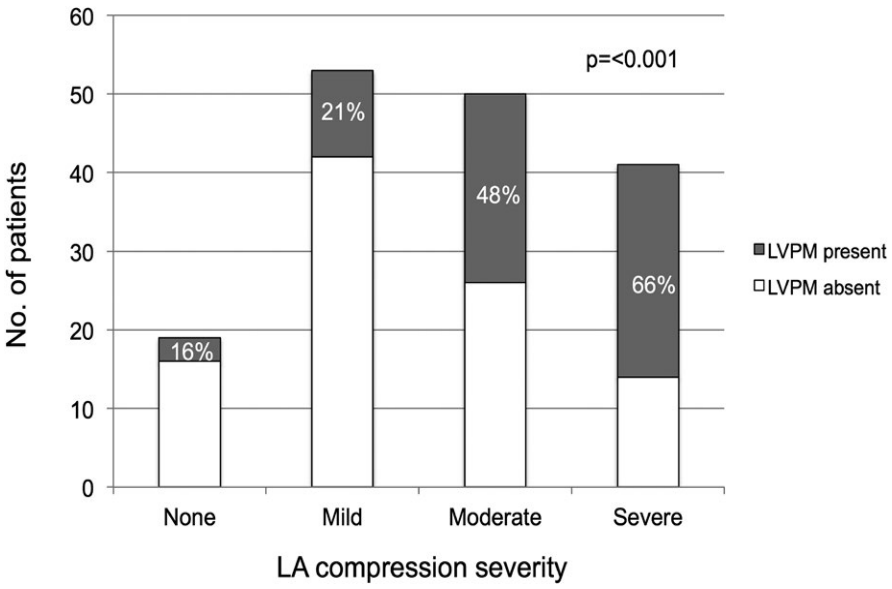


FIGURE 2 Left atrial compression and posterobasal left ventricular paradoxical motion. The number of patients within each LA compression severity grade is shown as well as the percentage of patients demonstrating LVPM within each category. Increasing LA compression severity was associated with a higher frequency of LV-PM ($P < .001$, chi-square test for trend)

m^2 vs 36 ± 10 mL/m^2, $P = .01$), and decreased LV stroke volume (21 ± 6 mL/m^2 vs 24 ± 6 mL/m^2, $P = .01$). Higher LA compression grades were also associated with increased systolic LA inflow velocity (83 ± 22 cm/s vs 71 ± 15 cm/s, $P = .0003$). LA diameter correlated inversely with systolic LA inflow velocity ($R = -0.24$, $P = .006$) and with diastolic LA inflow velocity but was only borderline significant ($R = -0.17$, $P = 0.05$).

The presence of LV-PM was also associated with decreased LA and LV dimensions; however, RVOT diameter was not reduced in patients with LV-PM. LV-PM predicted a greater reduction in biplane LV volume than did moderate–severe LA compression. Systolic LA inflow velocity was increased, and E-wave DT mildly prolonged in the presence of LV-PM. Mitral valve inflow velocities and RVSP did not correlate with either LA compression severity or the presence of LV-PM.

3.3 | Changes in echocardiographic parameters following surgery

Postoperative echocardiography was performed at a median of 78 (interquartile range, 51–103) days. LA and RVOT dimensions increased significantly following surgery; however, there was no significant change in LV dimensions (Table 3). LA inflow velocities and mitral E- and A-wave velocities all decreased significantly following surgery. The proportionately greater decrease in E-wave than A-wave velocity resulted in a reduced E/A ratio postoperatively (0.87 ± 0.23 preop vs 0.80 ± 0.19 postop, $P = .006$). LV stroke volume did not change significantly postoperatively, however, resting heart rate decreased significantly (75 ± 11 bpm preop and 72 ± 12 bpm postop, $P = .04$). RVSP did not change following HH surgery.

The magnitude of improvement in LA and RVOT dimensions postoperatively was greater among patients with moderate–severe LA compression than in those with none–mild LA compression; however, biplane LV volume changes postoperatively were not predicted by baseline LA compression (Table S4). Systolic and diastolic LA inflow velocities only decreased significantly postoperatively in patients with moderate–severe baseline LA compression. Interestingly, mitral E-wave velocity decreased significantly irrespective of baseline LA compression; however, a slightly greater degree of reduction was observed among patients with more severe LA compression. In addition, only patients with moderate–severe LA compression demonstrated a significant reduction in E/A ratio (0.87 ± 0.20 preop vs 0.78 ± 0.20 postop, $P = .01$). Whereas moderate–severe LA compression did not predict recovery of LV volumes after surgery, preoperative LV-PM did predict an increase in biplane LV volumes with surgery (Table S5). HH surgery reduced LA and mitral inflow velocities regardless of the presence or absence of preoperative LV-PM. Heart rate reduction was only observed in patients with moderate–severe LA compression or LV-PM. RVSP did not change following surgery irrespective of baseline LA compression or LVPM.

3.4 | Clinical and echocardiographic determinants of exercise capacity

At baseline, exercise testing was performed in 153 of 163 (94%) patients. Among these patients, univariable analysis showed that age, BMI, and the total number of cardiorespiratory comorbidities correlated negatively and male sex positively with exercise capacity (Table 4). LA and RVOT diameter, biplane LV diastolic volume, LV systolic volume, LV stroke volume, and E/A ratio correlated positively with exercise capacity. The severity of LA compression, the presence of LV-PM, average wall thickness, systolic LA inflow velocity, mitral E and A velocities, and RVSP correlated negatively with exercise capacity. On multivariable analysis, LA compression severity ($\beta = -.21$, $P = .002$) and RVOT diameter ($\beta = .15$, $P = .02$) were independently associated with exercise capacity (overall adjusted $R^2 = 0.56$, $P < .001$).

4 | DISCUSSION

The present study represents the largest reported cohort of patients with large HH evaluated using echocardiography and exercise

TABLE 3 Change in cardiac parameters following surgery

	Preop N = 72	Postop N = 72	*P*-value
LA diameter index—mm/m^2	14 ± 5	20 ± 4	<.0001
LV diastolic diameter index—mm/m^2	22 ± 3	23 ± 3	.39
LV systolic diameter index—mm/m^2	12 ± 3	12 ± 3	.90
Average wall thickness index—mm/m^2	5.8 ± 1.1	5.7 ± 1.0	.48
Fractional shortening—%	45 ± 10	45 ± 11	.81
LV diastolic volume index—mL/m^2	34 ± 10	35 ± 9	.13
LV systolic volume index—mL/m^2	12 ± 5	13 ± 4	.21
LV stroke volume index—mL/m^2	22 ± 6	23 ± 6	.43
LV ejection fraction—%	65 ± 8	65 ± 8	.65
Heart rate—bpm	75 ± 11	72 ± 12	.04
RVOT diameter/ BSA—mm/m^2	N = 67 17 ± 3	N = 67 19 ± 3	<.0001
Left atrial inflow	N = 54	N = 54	
S-wave—cm/s	78 ± 18	66 ± 13	.0001
D-wave—cm/s[a]	55 ± 17	45 ± 14	.0003
S/D ratio	1.47 ± 0.37	1.54 ± 0.35	.36
Mitral valve inflow	N = 56	N = 56	
E-wave—cm/s	73 ± 15	63 ± 14	<.0001
A-wave—cm/s	87 ± 20	81 ± 19	.002
E/A ratio	0.87 ± 0.23	0.80 ± 0.19	.006
DT—ms	205 ± 40	215 ± 45	.10
RV systolic pressure—mm Hg	N = 42 32 ± 7	N = 42 32 ± 9	.63

[a]BSA = body surface area. Diastolic LA inflow velocity measurable in 50 patients before and after surgery.

testing. In patients with HH, impaired exercise capacity is associated with a significant reduction in maximal LA and RVOT dimensions, posterobasal LV-PM and increased LA inflow, and transmitral filling velocities. Importantly, all of these parameters, including exercise capacity, improved following HH surgery. Multivariable analysis showed that echocardiographic assessment of LA compression severity and RVOT diameters were independently associated with exercise capacity in patients with large HH.

4.1 | Left atrial compression and the implications for left atrial and ventricular filling

Maximal LA diameter was significantly decreased in HH patients preoperatively, particularly in patients with higher grades of LA compression, and improved significantly following HH surgery. Despite significant LA compression, LV volumes were minimally affected. These results are consistent with our previous report that HH reduces three-dimensional maximal LA volumes on cardiac CT without affecting LV filling at rest because of relatively preserved LA emptying.[19]

In the present study, LA compression correlated with *baseline* exercise capacity independent of cardiorespiratory comorbidities, suggesting a possible causal relationship between HH-related compression and dyspnea. LA compression has been associated with cardiac symptoms in prior reports due to compression by HH[2–8,20–24] as well as other posterior mediastinal masses.[25–27] Potential mechanisms of exercise impairment secondary to LA compression include an inability of the LA to reach its maximal size, particularly during exercise when LA size increases to accommodate a larger reservoir volume.[28] Additionally, impaired LA physical distensibility due to HH may produce dyspnea in a manner similar to that observed with reduced LA compliance.[29–31]

Our data suggest that increased LA inflow velocities in HH patients are at least in part related to the hemodynamic effect of reducing the LA inflow cross-sectional area. Systolic LA inflow velocity correlated inversely with LA diameter preoperatively, and both systolic and diastolic LA inflow velocities only decreased significantly following surgery in patients with moderate–severe baseline LA compression. Increased systolic and diastolic pulmonary venous velocities have been similarly reported in association with cardiac compression by posterior mediastinal masses[32,33] and in pulmonary vein stenosis.[34] Our prior finding of inferior pulmonary venous compression by HH further supports this hypothesis.

While baseline E-wave velocity was not significantly associated with the degree of baseline LA compression or LV-PM, there was a significant reduction in the E-wave velocity postoperatively, which appeared to be greater in patients with moderate–severe LA compression. Early peak transmitral velocity reflects the LA-LV filling gradient.[35] Extrinsic compression of the LA by HH may potentially affect LA pressure and compliance, thereby enhancing the LA-LV filling gradient and accounting for the observed increase in mitral inflow velocities. These findings are consistent with our prior CT studies that showed enhanced passive LA emptying function in the presence of LA compression by HH.[19]

While mitral A-wave velocity also decreased following surgery, E-wave velocity appeared to decrease more significantly following surgery resulting in a decreased E/A ratio, especially in those with moderate–severe baseline LA compression. Given the E/A ratio is a noninvasive correlate of mean LA pressure,[36] these results may indicate that the LA-LV filling gradient is augmented by increased LA pressure in HH patients, and this is reduced by surgery. Prior reports of posture-related elevations of LA pressure in HH patients[5,7] support this hypothesis.

4.2 | Effects on right ventricular dimensions

The present study is the first to report that HH reduces RVOT diameter and that this improves postoperatively. Importantly, baseline

TABLE 4 Clinical and echocardiographic predictors of exercise capacity

	Univariable		Multivariable[a]	
	R value	*P*-value	β value	*P*-value
Clinical parameters				
Age	−0.47	<.001	−.55	<.001
BMI	−0.19	.02	−.31	<.001
Male sex	0.35	<.001	.19	.002
Total no. of cardiorespiratory comorbidities[b]	−0.22	.006	−.16	.01
Echocardiographic parameters				
Left atrial compression severity grade	−0.36	<.001	−.21	.002
Presence of LVPM	−0.20	.01	NS	NS
LA diameter index—mm/m^2	0.26	.001		
LV diastolic diameter index—mm/m^2	0.13	.12		
LV systolic diameter index—mm/m^2	0.07	.40		
Average wall thickness index—mm/m^2	−0.19	.02		
Fractional shortening—%	0.007	.93		
LV diastolic volume index—mL/m^2	0.20	.01		
LV systolic volume index—mL/m^2	0.22	.006		
LV stroke volume index—mL/m^2	0.16	.04		
LV ejection fraction—%	−0.14	.09		
Heart rate—bpm	−0.12	.13		
LV diastolic mass index—g/m^2	0.05	.53		
RV outflow tract diameter index—mm/m^2	0.27	.0009	.15	.02
Atrial inflow				
S-wave—cm/s	−0.23	.007	NS	NS
D-wave—cm/s	−0.10	.26		
S/D ratio	−0.15	.09		
Mitral valve inflow				
E-wave—cm/s	−0.21	.01	NS	NS
A-wave—cm/s	−0.39	<.001	NS	NS
E/A ratio	0.18	.03		
DT—ms	−0.08	.33		
RV systolic pressure—mm Hg	−0.31	.001		

BSA = body surface area; NS = not significant.

[a]Multivariable analysis (adjusted for age, BMI, sex, and total number of cardiorespiratory comorbidities) was performed including LA compression grade, LV paradoxical motion, RVOT diameter, systolic LA inflow velocity, and mitral E- and A-wave velocity by stepwise regression. LA diameter and E/A ratio were not included due to collinearity with LA compression severity (R = −0.71) and E-wave velocity (R = 0.51), respectively.

[b]Current or prior history of chronic obstructive pulmonary disease, asthma, pulmonary emboli, obstructive sleep apnea, other respiratory disease, smoking, ischemic heart disease, congestive heart failure, atrial arrhythmia, moderate or severe valvular heart disease, hypertension.

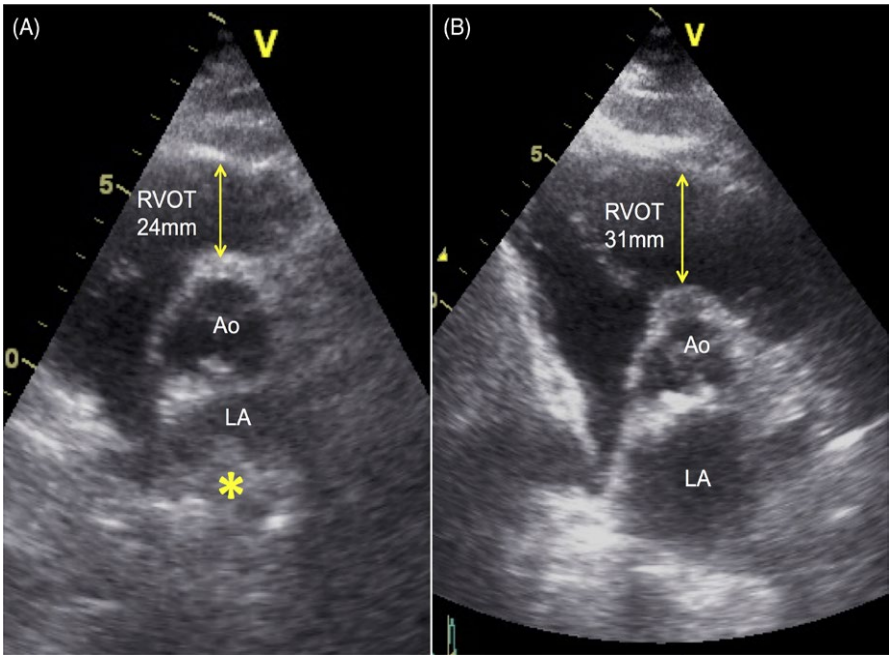


FIGURE 3 Change in right ventricular outflow tract diameter following HH surgery. Posterior cardiac compression by a HH (*) and reduction in the anteroposterior RVOT diameter are shown in panel A, with resolution of the posterior compression and increased RVOT diameter postoperatively in panel B

RVOT diameter was independently associated with exercise capacity. Reduced RVOT dimensions in the presence of HH may be explained by anterior cardiac displacement and compression of the RV against the anterior chest wall, particularly if the HH is located centrally in the posterior mediastinum (Figure 3).

Large masses can compress the heart between the posterior mediastinum and the anterior chest wall, leading to hemodynamic disturbances similar to circumferential pericardial tamponade.[37] RV compression caused by reduced anteroposterior diameter in pectus excavatum results in distorted RV geometry and is characterized by reduction in the RV short-axis diameter, lengthening of its long-axis diameter, and reduced RV ejection fraction compared to controls.[38] Exercise impairment is common in these patients and improves following surgical correction.[39,40] RV effects related to HH may therefore have an important role in the pathophysiological mechanism of dyspnea in this population.

4.3 | Left ventricular paradoxical motion

LV-PM was present in 40% of our patients at baseline and increased in frequency with increasing grades of LA compression severity (Figure 2). Encroachment of the atrioventricular groove resulting in LV-PM was previously noted in 10% of a small cohort of HH patients.[12] Differences in the reported prevalence may reflect differences in the size and severity of HH and prandial state of the patients studied in the 2 cohorts as well as differences in the subjective assessment of LV-PM between observers. The mechanism of LV-PM in HH patients is unknown; however, prior studies of patients with inferior LV wall compression by a raised hemidiaphragm have also demonstrated apparent pseudodyskinesis of this wall.[41] In these patients, a characteristic finding was flattening of the LV wall in diastole and restoration of the normal rounded contour in systole. In HH patients, extrinsic compression of the posterobasal LV wall may similarly result in pseudodyskinesis of this segment. Despite its ability to predict improved LV volumes following surgery, LV-PM was not independently associated with exercise capacity. This may of course be due to the binary definition for LV-PM used in this study, and future studies taking into consideration the magnitude of LV-PM and its possible impact on LV filling are needed.

4.4 | Limitations

The first limitation of this study is the selection of patients with large HH referred for cardiac assessment. Patients that returned for postoperative assessment appeared to have more significant cardiac compression preoperatively (Table S3) compared to patients that did not return for postoperative assessment. This limits the applicability of the study results to only those patients with large HH and significant baseline cardiac compression. Second, the echocardiographic analysis was not performed with the observer blinded to the patients' operative status as this was immediately apparent on echocardiography in most patients. Third, while RVOT diameter is likely to be a sensitive measure for detecting changes in RV chamber size due to HH given the anteroposterior direction of compression and displacement by posterior HH, measurement of additional RV dimensions including long-axis diameter and RV volume using CT or MRI would more appropriately characterize the nature of RV distortion and impact on RV filling. Finally, while patients were advised to consume a meal prior to presenting for their evaluation, feeding was not standardized in this study. Feeding in healthy subjects results in changes to commonly measured Doppler echocardiographic parameters.[42] However, the majority of echocardiographic parameters return to baseline 110 minutes following feeding, and this would have exceeded the interval between feeding and acquisition of Doppler echocardiography in

our study suggesting this is not likely to be a major factor in our study. Nevertheless, further studies are needed to evaluate the time-dependent impact of feeding on Doppler echocardiographic parameters in a large cohort of HH patients.

5 | CONCLUSIONS

This study represents the largest reported Doppler echocardiographic series of patients with large HH evaluated in relation to exercise capacity and before and after corrective HH surgery. We have shown that HH-related cardiac compression results in significantly reduced LA and RVOT dimensions. These parameters are independently associated with baseline exercise capacity and improve following HH surgery. Despite the reduction in LA and RV filling, E-wave velocity and E/A ratio are increased preoperatively and LV volumes are only mildly affected in the overall cohort at rest. LV-PM correlates with decreased LV volumes, which improve postoperatively, but is not independently associated with baseline exercise capacity in the HH population.

ACKNOWLEDGMENTS

The authors would like to thank Diana Hanzek and Zoya Pogrebizhsky for their assistance in performing the cardiac ultrasound studies.

ORCID

Christopher Naoum http://orcid.org/0000-0002-9910-2001

REFERENCES

1. Alkhouli M, Sandhu P, Wiegers SE, Patil P, Panidis J, Pursnani A. Extracardiac findings on routine echocardiographic examinations. *J Am Soc Echocardiogr*. 2014;27:540–546.
2. Lindner U, Paetzel M, Haas CS. An unusual cause of dyspnea in a patient with prior mitral valve annuloplasty and congestive heart failure. *J Thorac Cardiovasc Surg*. 2011;141:1313–1314.
3. Baerman JM, Hogan L, Swiryn S. Diaphragmatic hernia producing symptoms and signs of a left atrial mass. *Am Heart J*. 1988;116:198–200.
4. Moore JP, Fraser JF. Outside the box: extra-pericardial tamponade due to acute recurrence of hiatus hernia. *Ann Thorac Surg*. 2010;89:1654–1656.
5. Neumann L, Poulton B, Ridley S. Life-threatening complications of hiatus hernia. *Anaesthesia*. 1999;54:93–94.
6. Zwermann L, Rittler P, Spelsberg F, Helck A, Pratschke S, Methe H. Syncope due to a massive upside-down stomach. *J Am Coll Cardiol*. 2013;61:1925.
7. Raza ST, Mukherjee SK, Danias PG, et al. Hemodynamically significant extrinsic left atrial compression by gastric structures in the mediastinum. *Ann Intern Med*. 1995;123:114–116.
8. Devbhandari MP, Khan MA, Hooper TL. Cardiac compression following cardiac surgery due to unrecognised hiatus hernia. *Eur J Cardiothorac Surg*. 2007;32:813–815.
9. Akdemir I, Davutoglu V, Aktaran S. Giant hiatal hernia presenting with stable angina pectoris and syncope–a case report. *Angiology*. 2001;52:863–865.
10. Oishi Y, Ishimoto T, Nagase N, et al. Syncope upon swallowing caused by an esophageal hiatal hernia compressing the left atrium: a case report. *Echocardiography*. 2004;21:61–64.
11. Nishimura RA, Tajik AJ, Schattenberg TT, Seward JB. Diaphragmatic hernia mimicking an atrial mass: a two-dimensional echocardiographic pitfall. *J Am Coll Cardiol*. 1985;5:992–995.
12. D'Cruz IA, Hancock HL. Echocardiographic characteristics of diaphragmatic hiatus hernia. *Am J Cardiol*. 1995;75:308–310.
13. Naoum C, Falk GL, Ng AC, et al. Left atrial compression and the mechanism of exercise impairment in patients with a large hiatal hernia. *J Am Coll Cardiol*. 2011;58:1624–1634.
14. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.
15. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713; quiz 86–88.
16. Anderson B. *Echocardiography: The Normal Examination and Echocardiographic Measurements*, 2nd edn. Brisbane, Australia: MGA Graphics; 2007.
17. Bruce RA. Exercise testing of patients with coronary heart disease. Principles and normal standards for evaluation. *Ann Clin Res*. 1971;3:323–332.
18. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J*. 1973;85:546–562.
19. Naoum C, Kritharides L, Thomas L, et al. Modulation of phasic left atrial function and left ventricular filling in patients with extrinsic left atrial compression by hiatal hernia. *Int J Cardiol*. 2014;176:1176–1178.
20. Siu CW, Jim MH, Ho HH, et al. Recurrent acute heart failure caused by sliding hiatus hernia. *Postgrad Med J*. 2005;81:268–269.
21. Gupta M, Nanda NC, Inamdar V. Two- and three-dimensional transthoracic echocardiographic assessment of hiatal hernia. *Echocardiography*. 2008;25:790–793.
22. Smelley M, Lang RM. Large mass impinging on the left atrium: diagnostic value of a new cocktail. *J Am Soc Echocardiogr*. 2007;20:1414. e5–7.
23. Clark T, Pearson D, Macnaughton P. A rare cause of cardiogenic shock. *Intensive Care Med*. 2012;38:1569–1570.
24. Tadler SC, Burton JH. Intrathoracic stomach presenting as acute tension gastrothorax. *Am J Emerg Med*. 1999;17:370–371.
25. Iwase M, Nagura E, Miyahara T, Goto J, Kajita M, Yamada H. Malignant lymphoma compressing the heart and causing acute left-sided heart failure. *Am Heart J*. 1990;119:968–970.
26. Faletra F, Ravini M, Moreo A, et al. Transesophageal echocardiography in the evaluation of mediastinal masses. *J Am Soc Echocardiogr*. 1992;5:178–186.
27. Liao ZY, Tsai JP, Kuo JY, Hung CL. Large aortic aneurysm mimicking a cardiac tumor. *Cardiovasc Ultrasound*. 2010;8:33.
28. Furukawa K, Kitamura H, Nishida K, et al. Simultaneous changes of left ventricular and left atrial size and function in normal subjects during exercise. *Jpn Heart J*. 1984;25:487–497.
29. Mehta S, Charbonneau F, Fitchett DH, Marpole DG, Patton R, Sniderman AD. The clinical consequences of a stiff left atrium. *Am Heart J*. 1991;122:1184–1191.
30. Witt C, Powell B, Holmes D, Alli O. Recurrent dyspnea following multiple ablations for atrial fibrillation explained by the "stiff left atrial syndrome". *Catheter Cardiovasc Interv*. 2012;82:E747–E749.

31. Park S, Ha JW, Ko YG, et al. Magnitude of left atrial V wave is the determinant of exercise capacity in patients with mitral stenosis. *Am J Cardiol*. 2004;94:243–245.
32. Sadaniantz A, Pyne CT. Obstruction of left atrial filling by a large descending thoracic aortic aneurysm detected by pulsed doppler echocardiography. *Echocardiography*. 1994;11:323–326.
33. Ren WD, Nicolosi GL, Lestuzzi C, et al. Role of transesophageal echocardiography in evaluation of pulmonary venous obstruction by paracardiac neoplastic masses. *Am J Cardiol*. 1992;70:1362–1366.
34. Tabata T, Thomas JD, Klein AL. Pulmonary venous flow by doppler echocardiography: revisited 12 years later. *J Am Coll Cardiol*. 2003;41:1243–1250.
35. Little WC, Oh JK. Echocardiographic evaluation of diastolic function can be used to guide clinical care. *Circulation*. 2009;120:802–809.
36. Kuecherer HF, Muhiudeen IA, Kusumoto FM, et al. Estimation of mean left atrial pressure from transesophageal pulsed Doppler echocardiography of pulmonary venous flow. *Circulation*. 1990;82:1127–1139.
37. D'Cruz IA, Feghali N, Gross CM. Echocardiographic manifestations of mediastinal masses compressing or encroaching on the heart. *Echocardiography*. 1994;11:523–533.
38. Saleh RS, Finn JP, Fenchel M, et al. Cardiovascular magnetic resonance in patients with pectus excavatum compared with normal controls. *J Cardiovasc Magn Reson*. 2010;12:73.
39. Neviere R, Montaigne D, Benhamed L, et al. Cardiopulmonary response following surgical repair of pectus excavatum in adult patients. *Eur J Cardiothorac Surg*. 2011;40:e77–e82.
40. Haller JA Jr, Loughlin GM. Cardiorespiratory function is significantly improved following corrective surgery for severe pectus excavatum. Proposed treatment guidelines. *J Cardiovasc Surg (Torino)*. 2000;41:125–130.
41. Yosefy C, Levine RA, Picard MH, Vaturi M, Handschumacher MD, Isselbacher EM. Pseudodyskinesis of the inferior left ventricular wall: recognizing an echocardiographic mimic of myocardial infarction. *J Am Soc Echocardiogr*. 2007;20:1374–1379.
42. Dencker M, Bjorgell O, Hlebowicz J. Effect of food intake on commonly used pulsed Doppler and tissue Doppler measurements. *Echocardiography*. 2011;28:843–847.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1. Intra- and inter-observer agreement for LA and RVOT diameter measurements in HH patients

Table S2. Clinical variables stratified by whether patients underwent post-operative evaluation

Table S3. Echocardiographic variables stratified by whether patients underwent post-operative evaluation

Table S4. Echocardiographic changes following surgery stratified by LA compression severity

Table S5. Echocardiographic changes following surgery stratified by the presence of LV-PM

Movie S1. Parasternal long-axis view in a patient with a large HH (**) showing paradoxical early systolic outward motion of the basal LV due to extrinsic compression by the HH.

Movie S2. Parasternal long-axis view from the same patient in video 1A following HH surgery showing resolution of preoperative LV paradoxical motion.

How to cite this article: Naoum C, Kritharides L, Falk GL, Martin D, Yiannikas J. Left atrial compression and right ventricular outflow tract diameter on echocardiography are independently associated with exercise capacity in patients with large hiatal hernia. *Echocardiography*. 2018;35:592–602. https://doi.org/10.1111/echo.13835

The Clinical Respiratory Journal ORIGINAL ARTICLE

Changes in lung volumes and gas trapping in patients with large hiatal hernia

Christopher Naoum[1], Leonard Kritharides[1], Alvin Ing[2], Gregory L. Falk[3] and John Yiannikas[1]

1 Department of Cardiology, Concord Repatriation General Hospital, The University of Sydney, Sydney, New South Wales, Australia
2 Department of Respiratory Medicine, Concord Repatriation General Hospital, The University of Sydney, Sydney, New South Wales, Australia
3 Department of Upper GI Surgery, Concord Repatriation General Hospital, The University of Sydney, Sydney, New South Wales, Australia

Abstract

Background and Aims: Studies assessing hiatal hernia (HH)-related effects on lung volumes derived by body plethysmography are limited. We aimed to evaluate the effect of hernia size on lung volumes (including assessment by body plethysmography) and the relationship to functional capacity, as well as the impact of corrective surgery.

Methods: Seventy-three patients (70 ± 10 years; 54 female) with large HH [mean ± standard deviation, intra-thoracic stomach (ITS) (%): 63 ± 20%; type III in 65/73] had respiratory function data (spirometry, 73/73; body plethysmography, 64/73; diffusing capacity, 71/73) and underwent HH surgery. Respiratory function was analysed in relation to hernia size (groups I, II and III: ≤50, 50%–75% and ≥75% ITS, respectively) and functional capacity. Post-operative changes were quantified in a subgroup.

Results: Total lung capacity (TLC) and vital capacity (VC) correlated inversely with hernia size (TLC: 97 ± 11%, 96 ± 13%, 88 ± 10% predicted in groups I, II and III, respectively, $P = 0.01$; VC: 110 ± 17%, 111 ± 14%, 98 ± 14% predicted, $P = 0.02$); however, mean values were normal and only 14% had abnormal lung volumes. Surgery increased TLC (93 ± 11% vs 97 ± 10% predicted) and VC (105 ± 15% vs 116 ± 18%), and decreased residual volume/total lung capacity (RV/TLC) ratio (39 ± 7% vs 37 ± 6%) ($P < 0.01$ for all). Respiratory changes were modest relative to the marked functional class improvement. Among parameters that improved following HH surgery, decreased TLC and forced expiratory volume in 1 s and increased RV/TLC ratio correlated with poorer functional class pre-operatively.

Conclusions: Increasing HH size correlates with reduced TLC and VC. Surgery improves lung volumes and gas trapping; however, the changes are mild and within the normal range.

Please cite this paper as: Naoum C, Kritharides L, Ing A, Falk GL and Yiannikas J. Changes in lung volumes and gas trapping in patients with large hiatal hernia. *Clin Respir J* 2017; 11: 139–150. DOI:10.1111/crj.12314.

Key words
dyspnoea – hiatal hernia – lung compression – lung volume – respiratory function

Correspondence
John Yiannikas, MBBS, Department of Cardiology, Concord Hospital, Hospital Road, 2139 Concord, NSW, Australia.
Tel: +61 2 9767 6296
Fax: +61 2 9767 8395
email: john.yiannikas@sydney.edu.au

Received: 13 October 2014
Revision requested: 15 April 2015
Accepted: 21 April 2015

DOI:10.1111/crj.12314

Authorship and contributorship
All authors contributed to study conception and data analysis. CN drafted the manuscript, which was revised by all authors.

Ethics
The Sydney Local Health District Human Research Ethics Committee approved the collection, analysis and reporting of data.

Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

Introduction

Patients with large hiatal hernia (HH) are frequently affected by dyspnoea, although the association is seldom recognised clinically (1). Some studies have reported a correlation between dyspnoea and increasing hernia size as well as a symptomatic improvement following surgical repair, suggesting a direct causal relationship between dyspnoea and the space-occupying effect of the hernia (2–4).

There are few data however regarding the space-occupying respiratory effects of large HH within the thorax and the potential contribution of these abnormalities to dyspnoea symptoms. Mixed results have been observed in prior studies with mildly reduced spirometric parameters and lung diffusing capacity

demonstrated in some reports (2, 3) but not in others (4). Early studies reported no significant correlation between HH size and spirometry although reduced lung ventilation and perfusion were demonstrated, particularly in basal segments adjacent to the hernia (5, 6). We have also investigated cardiac and respiratory abnormalities in HH patients and demonstrated a modest improvement in respiratory function in patients with large HH undergoing surgical repair; however, mean baseline values were within the normal range (7). Our previous study was limited by the relatively small sample size and lack of detailed analyses of lung volume subsets, which are pertinent to the space-occupying effects of HH.

Accordingly, the present study had two aims: first, to elucidate the space-occupying respiratory effects of HH and the relationship between HH-related respiratory dysfunction and functional capacity; and second, to quantify the improvement in respiratory function following HH surgery.

Materials and methods

Patients with a HH referred for cardiac evaluation between May 2009 and February 2012 were entered into a database ($n = 103$). All patients that underwent formal laboratory respiratory function testing (RFT) as part of their routine pre-operative evaluation and who proceeded to surgical HH repair were included in this analysis. Demographic details, New York Heart Association (NYHA) functional class and co-morbidities were identified from the clinical evaluation. Two primary analyses were performed: first, baseline respiratory function was analysed in relation to both HH size and NYHA functional class; second, changes in respiratory function following surgery were quantified in a subgroup that underwent HH surgery and post-operative RFT. Data from a subgroup of this cohort have been previously reported (7). The Sydney Local Health District Human Research Ethics Committee approved the collection and reporting of data.

RFT

Lung volumes (via body plethysmography), spirometry and single-breath diffusing capacity of lung for carbon monoxide (DLCO) were performed according to American Thoracic Society criteria using a commercially available system (Vmax Encore; SensorMedics, Yorba Linda, CA, USA) (8–10). Normal lung volumes were defined as total lung capacity (TLC) above 80% of predicted and residual volume (RV) below 120% of predicted. Airways resistance (Raw) and specific conductance (sGAW) were also measured using body plethysmography in a subgroup of patients. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria were used to define normal airflow (11). Whenever possible, repeat spirometry was performed following the administration of 400 mcg of inhaled salbutamol via a spacer to assess for reversible airways obstruction as previously described (12). DLCO and DLCO corrected for alveolar volume (DLCO/Va) were considered abnormal if less than 70% of predicted (13). RFT was performed under normal conditions without prior oral loading as per standard respiratory laboratory protocol.

Surgical repair and HH sizing and classification

HH repair was achieved laparoscopically in the majority of patients and involved sac excision, suture repair of the crural pillars, esophagogastropexy and 360° fundoplication (14). HH size was documented in the surgical report using the intra-thoracic stomach (ITS %) value. This measure represents the percentage of stomach that has been displaced through the diaphragmatic hiatus into the thorax and is consistent with sizing nomenclature used in prior HH studies (1, 3). The surgeon estimated ITS (%) based on the anatomical relationship between gastric landmarks and the diaphragmatic hiatus. The assessment was based on review of clinically available imaging studies (contrast studies and/or endoscopy) performed prior to surgery and/or direct visualisation of the operative findings at the time of surgery. HH type (I, II, III and IV) was classified according to current guidelines for the management of HH (15).

Statistical analysis

Data are expressed as mean ± standard deviation or number (percentage). Non-parametric data are also expressed as median [interquartile range (IQR)] in the tables. RFT values are expressed as a percentage of age- and gender-predicted values. Absolute lung volumes are also reported in the paired comparisons before and after surgery. Patients were divided into three groups at baseline according to the percentage of ITS (group I: ≤50% ITS, group II: 50%–75% ITS, group III: ≥75%–100% ITS). Continuous RFT data were compared between groups using a one-way analysis of variance (ANOVA). For variables with ANOVA $P < 0.05$, a post-test analysis for linear trend was also performed. Categorical variables were compared between HH groups at baseline using a chi-squared test for trend. Baseline

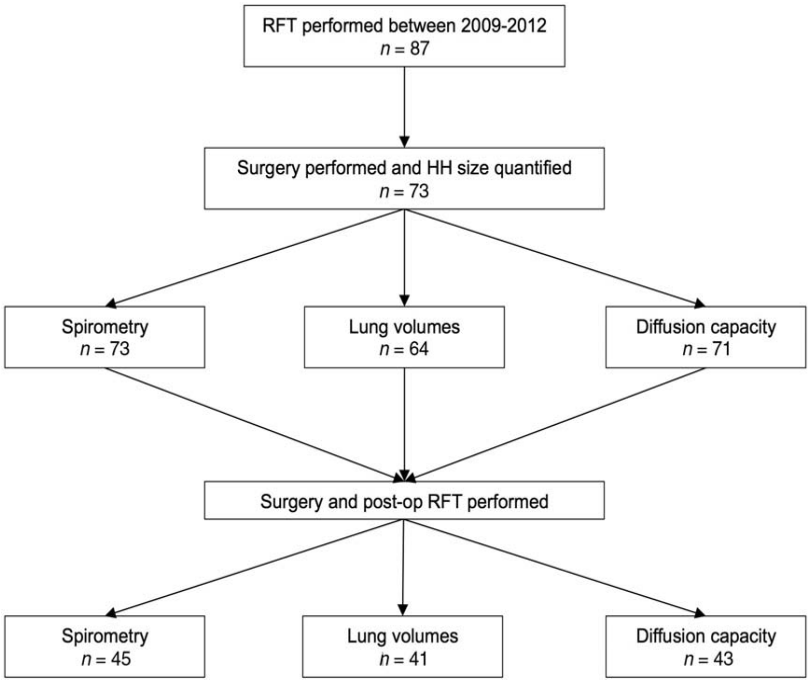


Figure 1. Study flow chart defining pre- and post-operative cohorts.

RFT parameters were also analysed in relation to the severity of symptoms (NYHA class I-II vs III-IV) using an unpaired *t*-test or Mann–Whitney test as appropriate. Following surgery, paired analyses of respiratory parameters for the overall group and according to baseline HH size were performed using a paired *t*-test or Wilcoxon matched pairs test as appropriate for continuous variables and a McNemar test for dichotomous variables. Changes in NYHA class after surgery were analysed using a Wilcoxon matched-pairs test. Statistical analyses were performed using GraphPad Prism Version 6.0d (GraphPad Software, La Jolla, CA, USA). A *P* value of less than 0.05 was considered statistically significant.

Results

Between May 2009 and February 2012, 87/103 (84%) patients with HH referred for cardiac evaluation underwent RFT. Of these, 73/89 (82%) patients proceeded to surgical repair with estimation of the ITS (%) available in the surgical report. Body plethysmography lung volumes were obtained in 64 of 73 patients, DLCO in 71 of 73 patients and spirometry in all patients (Fig. 1). RFT was performed at a median (IQR) of 74 (39–114) days pre-operatively.

Baseline clinical characteristics of the study cohort are presented in Table 1. The majority of patients reported exertional dyspnoea consistent with either NYHA class II or III symptoms. The most frequently reported respiratory co-morbidities included asthma, sleep apnoea and chronic obstructive pulmonary disease. The majority of patients (65/73, 89%) had a type III hernia and ITS values were consistent with a large HH (ITS > 50%) in 45/73 (61%) patients (Fig. 2).

Baseline RFT values are reported in Table 2. Although most patients had a large HH, mean lung volume, spirometric and DLCO values were within normal limits. There were only 9/64 (14%) patients that met criteria for abnormal lung volumes (seven with reduced TLC and two with increased RV). Obstructive spirometry [forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio <70%] was observed in 28/73 (38%) patients, with most affected patients demonstrating mild obstruction only (20/28) and the remainder demonstrating moderate obstruction (8/28). Moreover, when expressed as a percentage of predicted values, FEV_1/FVC was normal overall (96 ± 11% of predicted) and no patients had an FEV_1/FVC below 70% of predicted. Reversible airways obstruction was present in 7/62 (11%) patients that underwent repeat spirometry following bronchodilator, among whom only 2/7 (29%) had a prior history of asthma. Conversely, of the 12 patients reporting a prior history of asthma, reversibility testing was performed in 11, of whom only 2/11 (18%) met criteria for reversible airways obstruction. Reduced DLCO and DLCO/Va were observed in a significant number of patients (32% and 38%, respectively). Of these

Table 1. Baseline characteristics

Demographics	*n* = 73
Age – year ± SD	70 ± 10
Female gender – *n* (%)	54 (74)
Body mass index (kg/m^2)	30.6 ± 5.4
Dyspnoea	
Exertional*	55 (76)
Postprandial	39 (53)
NYHA class†	
Class I	17 (24)
Class II	18 (26)
Class III	31 (44)
Class IV	4 (6)
Respiratory co-morbidities – *n* (%)	
Chronic obstructive pulmonary disease	5 (7)
Asthma	12 (16)
History of pulmonary emboli	4 (5)
Sleep apnoea	7 (10)
Current smoker	0 (0)
Ex-smoker	20 (27)
Other pulmonary disease‡	5 (7)
Use of inhaled bronchodilator and/or steroid	16 (22)
Other co-morbidities	
History of cardiac disease§	21 (29)
Diabetes	11 (15)
Hypertension	37 (51)
Dyslipidaemia	43 (59)
Hiatal hernia size and classification¶	
Mean ITS (%)	63 ± 20
ITS ≤ 50%	28 (38)
ITS 50%–75%	20 (27)
ITS ≥ 75%	25 (34)
Type I	1 (1)
Type II	0 (0)
Type III	65 (89)
Type IV	7 (10)

*Not classifiable in one patient due to paraplegia.

†Not classifiable in three patients due to paraplegia (*n* = 2) and significant musculoskeletal problems limiting function (*n* = 1).

‡Silicosis, aspiration pneumonitis, lung resection for cancer, basal pulmonary fibrosis and bronchitis.

§History of ischaemic heart disease, atrial arrhythmia, congestive heart failure or moderate or greater valvular heart disease.

¶Type I, sliding; type II, paraoesophageal; type III, mixed; type IV, mixed plus visceral herniation.

patients, prior smoking was reported in 12/23 (52%) and 11/27 (41%), respectively.

The relationship between HH size and respiratory function is presented in Table 2. TLC and vital capacity (VC) were decreased in patients with a larger HH; however, there was no significant difference in RV or RV/TLC ratio between groups. There was no relationship between HH size and FEV_1/FVC ratio. DLCO trended towards being decreased in patients with larger HH; however, this was not statistically significant and DLCO/Va was not different between groups.

Respiratory function is stratified by NYHA functional class in Table 3. Reduced FEV_1, forced expiratory $flow_{25\%–75\%}$, peak expiratory flow, TLC and DLCO, and increased RV/TLC ratio and Raw were associated with higher NYHA classification.

Following surgery, 45 of 73 patients underwent post-operative RFT at a median of 93 (78–126) days post-operatively (Fig. 1). There was a significant improvement in symptoms following surgery (NYHA class I, II, III and IV: 10/42, 14/42, 16/42 and 2/42 pre-operative and 38/42, 4/42, 0/42 and 0/42 post-operative, respectively, among patients with classifiable NYHA, $P < 0.001$). Post-operative changes in RFT are reported in Table 4. Surgery resulted in a significant increase in TLC, VC and expiratory reserve volume. RV/TLC ratio decreased following surgery suggesting reduced gas trapping. FEV_1 and FVC both improved following surgery with no significant change in FEV_1/FVC ratio. DLCO did not change significantly following surgery; however, there was a significant reduction in DLCO/Va.

In general, the improvement in respiratory parameters following surgery was greatest in patients with largest baseline HH (Table 5). VC, TLC, RV/TLC ratio, FEV_1, FVC and Raw decreased significantly in larger hernias only. Unlike other parameters, DLCO/Va decreased most significantly in group I and was of borderline significance in groups II and III, suggesting the improvement in DLCO/Va following HH surgery was independent of baseline HH size.

Of the RFT variables that changed significantly following surgery, reduced TLC and FEV_1 and increased RV/TLC ratio were observed in HH patients with poorer NYHA classification.

Discussion

The present study has evaluated the space-occupying effects of HH on thoracic lung volumes and the impact of surgical HH repair. The primary findings were that increasing hernia size was associated with reduced TLC and VC. Surgery resulted in an improvement of these lung volumes and a reduction in RV/TLC ratio consistent with reduced gas trapping. However, in the majority of patients, mean baseline lung volumes were within the normal range and the post-operative improvement in these volumes was modest compared with the significant improvement in NYHA functional class. These results suggest that the contribution of

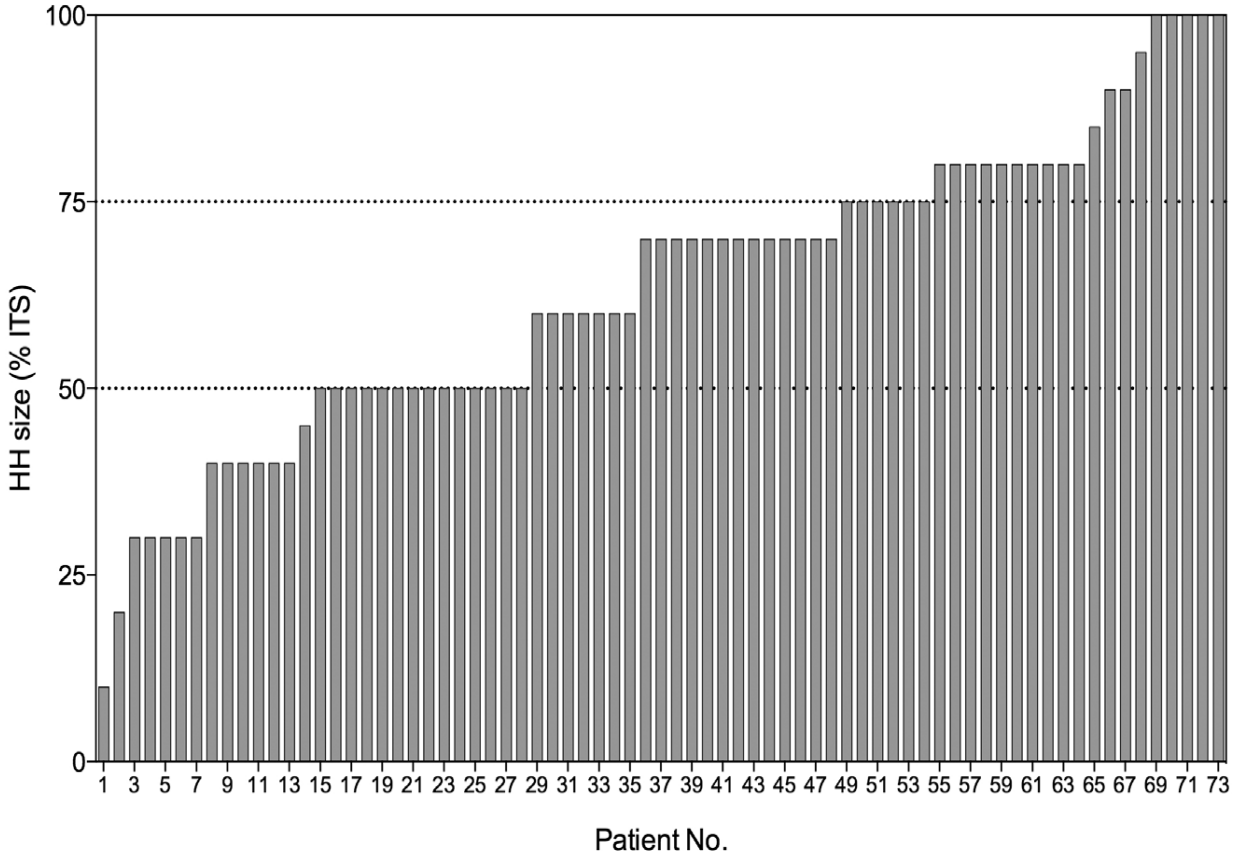


Figure 2. Hiatal hernia size of each patient presented in ascending order of the percentage of intra-thoracic stomach (%).

reduced lung volumes to dyspnoea symptoms may be minimal in the HH population.

Effects of HH on lung volumes

Mean baseline lung volumes were normal and only a few patients (14%) met the specified criteria for abnormal lung volumes. However, hernia size correlated inversely with both TLC and VC pre-operatively, and both of these parameters increased significantly following surgery. HH size also correlated with the magnitude of improvement in VC post-operatively. Reduced TLC in HH patients may be explained by the hernia producing a mild extra-parenchymal restrictive defect similar to that observed in patients with a large pleural effusion or pneumothorax (16), progressive cardiac enlargement due to heart failure (17), obesity (18), kyphoscoliosis (19), ascites (20) and pregnancy (21). Restrictive lung disease may also occur in HH patients because of pulmonary fibrosis associated with gastro-oesophageal reflux (22, 23). However, in our patients, although DLCO was reduced in 32% of patients, mean DLCO and TLC were normal suggesting that pulmonary fibrosis is an unlikely explanation. The pattern of change in spirometric parameters following surgery is also consistent with reduced extra-parenchymal restriction as both FEV_1 and FVC increased proportionately, particularly in the presence of large HH, with preservation of the FEV_1/FVC ratio. Mildly reduced FEV_1 and FVC values, which improve following surgery, have been demonstrated in prior studies of HH patients (2, 3).

The presence of a HH was also associated with increased RV/TLC ratio suggesting gas trapping. This appeared to be related to the size of the hernia, with the reduction in RV/TLC ratio post-operatively only observed in large HH patients. Increased RV, a measure of gas trapping, has been demonstrated in patients with variable HH sizes and types (5) and is typically observed in conditions associated with either loss of thoracic elastic recoil or dynamic airways obstruction or both. In our cohort, extrinsic lung compression by HH may have led to partial obstruction of the small non-cartilaginous airways resulting in gas trapping through a ball valve mechanism analogous to that observed in patients with extrinsic bronchial compression by bronchogenic cysts (24) or lung cancer (25). Alternatively, the increase in

Table 2. Baseline respiratory function stratified by hiatal hernia size

	All patients	Group I (ITS ≤ 50%)	Group II (ITS 50%–75%)	Group III (ITS ≥ 75%)	*P* value*
Spirometry	*n* = 73	*n* = 28	*n* = 20	*n* = 25	
FEV_1 – % predicted	95 ± 19	97 ± 22	99 ± 12	90 ± 17	0.17
FVC – % predicted	107 ± 18	108 ± 19	112 ± 13	100 ± 18	0.06
FEV_1/FVC	72 ± 9	74 ± 9	72 ± 8	72 ± 10	0.34
	72 (67–78)	73 (68–81)	74 (65–78)	71 (67–76)	
FEV_1/FVC – % predicted	96 ± 11	97 ± 11	95 ± 10	96 ± 13	0.66
	96 (89–103)	98 (90–105)	98 (88–102)	96 (89–100)	
$FEF_{25\%–75\%}$ – % predicted	60 ± 33	64 ± 31	55 ± 21	58 ± 42	0.45
	53 (37–74)	59 (39–89)	53 (35–68)	51 (35–64)	
Peak expiratory flow – % predicted	94 ± 21	94 ± 25	94 ± 16	93 ± 21	0.97
FEV_1/FVC < 70% – *n* (%)†	28/73	9/28	7/20	12/25	0.24
Reversible airways	*n* = 62	*n* = 23	*n* = 17	*n* = 22	
obstruction – *n* (%)‡	7/62	2/23	3/17	2/22	0.96
Lung volumes	*n* = 64	*n* = 24	*n* = 18	*n* = 22	
TLC – % predicted	94 ± 12	97 ± 11	96 ± 13	88 ± 10	0.01 (0.005)
VC – % predicted	106 ± 16	110 ± 17	111 ± 14	98 ± 14	0.02 (0.01)
RV – % predicted	88 ± 17	90 ± 20	90 ± 18	85 ± 12	0.54
Expiratory reserve volume – L	0.67 ± 0.39	0.66 ± 0.43	0.68 ± 0.43	0.66 ± 0.33	0.98
	0.59 (0.37–0.84)	0.61 (0.33–0.71)	0.55 (0.45–0.91)	0.61 (0.39–0.87)	
RV/TLC ratio	39 ± 7	37 ± 8	40 ± 5	41 ± 8	0.30
TLC < 80% predicted – *n* (%)	7/64	1/24	2/18	4/22	0.13
RV > 120% predicted – *n* (%)	2/64	2/24	0/18	0/22	0.10
Airway resistance/conductance	*n* = 56	*n* = 20	*n* = 17	*n* = 19	
Raw	1.87 ± 0.72	1.91 ± 0.73	1.68 ± 0.53	2.01 ± 0.84	0.51
	1.74 (1.34–2.28)	1.74 (1.34–2.39)	1.55 (1.31–1.96)	1.94 (1.25–2.62)	
sGaw	0.20 ± 0.06	0.19 ± 0.06	0.21 ± 0.04	0.19 ± 0.08	0.64
	0.20 (0.16–0.24)	0.20 (0.14–0.24)	0.20 (0.19–0.22)	0.17 (0.14–0.25)	
Diffusing capacity	*n* = 71	*n* = 28	*n* = 19	*n* = 24	
DLCO – % predicted	74 ± 14	78 ± 11	73 ± 14	71 ± 18	0.18
DLCO/Va – % predicted	75 ± 13	77 ± 13	73 ± 13	74 ± 14	0.59
	77 (65–83)	79 (66–84)	77 (66–84)	71 (63–83)	
DLCO < 70% predicted – *n* (%)	23/71	6/28	7/19	10/24	0.12
DLCO/Va < 70% predicted – *n* (%)	27/71	9/28	8/19	10/24	0.47

**P* value comparing means between three groups using an ordinary one-way ANOVA or Kruskal–Wallis test as appropriate for continuous variables. For variables with ANOVA $P < 0.05$, the *P* value in brackets represents the significance level of the post-test for linear trend. For categorical variables, *P* value for chi-square test for trend is reported.

†Airflow limitation defined as an FEV_1/FVC ratio less than 70% (11). In the presence of reduced FEV_1/FVC, the severity of airflow limitation was classified as mild ($FEV_1 \geq 80\%$ predicted), moderate ($30 \leq FEV_1 < 80\%$ % predicted) or severe ($FEV_1 < 30\%$ predicted).

‡Reversible airflow limitation was defined as a > 12% predicted (and >200 mL) improvement in either FEV_1 or FVC.

RV/TLC ratio pre-operatively may have been due to extra-parenchymal trapping of air within the hernia itself.

Effects of HH on airflow and reversibility following bronchodilator

Although there was a high prevalence of obstructive spirometry (as defined by the GOLD criteria) (11), when expressed in terms of predicted values, mean FEV_1/FVC was normal. Moreover, FEV_1/FVC ratio did not correlate with baseline HH size or change significantly following surgery. These data suggest that any apparent obstructive defect using the GOLD criteria, at least, are likely due to co-existing obstructive airways disease as has been previously suggested (26) rather than a space-occupying effect of the HH. The significantly higher rate of prior smoking in patients with a reduced FEV_1/FVC ratio compared with patients with a normal FEV_1/FVC ratio (12/28, 43% vs 8/45, 18%,

Table 3. Baseline respiratory parameters stratified by NYHA class

	NYHA class I-II	NYHA class III-IV	*P* value*
Spirometry	*n* = 35	*n* = 35	
FEV_1 – % predicted	100 ± 18	90 ± 19	0.03
FVC – % predicted	110 ± 18	103 ± 17	0.11
FEV_1/FVC	73 ± 9	71 ± 7	0.20
FEV_1/FVC – % predicted	97 ± 13	94 ± 9	0.36
$FEF_{25\%–75\%}$ – % predicted	70 ± 37	48 ± 23	0.002
	59 (48–90)	39 (33–57)	
Peak expiratory flow – % predicted	99 ± 24	87 ± 16	0.03
Lung volumes	*n* = 33	*n* = 29	
TLC – % predicted	98 ± 12	89 ± 10	0.0009
VC – % predicted	111 ± 17	102 ± 14	0.13
RV – % predicted	91 ± 18	85 ± 16	0.15
RV/TLC ratio	37 ± 7	41 ± 7	0.02
Airway resistance / conductance	*n* = 29	*n* = 25	
Raw	1.61 ± 0.67	2.15 ± 0.65	0.002
	1.42 (1.16–1.89)	2.17 (1.64–2.49)	
sGaw	0.21 ± 0.07	0.18 ± 0.05	0.12
Diffusing capacity	*n* = 34	*n* = 34	
DLCO – % predicted	80 ± 12	69 ± 15	0.002
DLCO/Va – % predicted	76 ± 11	73 ± 15	0.33

**P* values for unpaired *t*-test or Mann–Whitney test as appropriate.

respectively, $P = 0.03$) supports this hypothesis. Airways resistance, a more sensitive measure of airways obstruction, was also measured in a subgroup of patients. There was a decrease in Raw and borderline increase in sGaw in patients within the large HH group. Removal of a large HH from the thorax may improve elastic recoil and therefore airway conductance. However, the lack of a significant effect on Raw in the overall cohort suggests that any obstructive defect induced by the HH is likely to be mild.

Reversibility of airflow limitation was present in 11% of patients assessed following inhaled bronchodilator. HH has been associated with asthma previously because of aspiration of gastric refluxate and/or stimulation of oesophageal vagal nerve endings leading to bronchoconstriction through common neural pathways (27). The prevalence of asthma in our cohort however is similar to the prevalence of current asthma in the general adult Australian population (~10%) (28). Interestingly, among those reporting a prior history of asthma, only 18% demonstrated reversibility following administration of a bronchodilator. We have anecdotally noted a significant rate of asthma diagnosis in these patients however with minimal symptomatic response to bronchodilators pre-operatively and frequent cessation of bronchodilator use post-operatively, suggesting potential misdiagnosis of dyspnoea in this population.

Effects of HH on lung diffusion capacity

Baseline DLCO was decreased in a significant proportion of patients (32%); however, there was no significant correlation between HH size and DLCO and, unlike prior studies (3), DLCO did not improve following HH repair in our cohort. The mild impairment of DLCO in our patients is therefore likely to be due to co-existing respiratory disease. This is again supported by the observation of a high rate of prior smoking in the patients with reduced DLCO.

Surgery resulted in a decrease in DLCO/Va, which may be explained by re-expansion of compressed lung segments adjacent to the HH post-operatively leading to increased alveolar volume (Fig. 3). However, unlike the changes observed in lung volumes, DLCO/Va reduction post-operatively did not appear to correlate with hernia size, and apart from lung compression, reduced body weight in the early post-operative phase may have also contributed to decreased DLCO/Va.

The relationship between respiratory function and symptoms

NYHA class improved following HH surgery similar to the improvement in dyspnoea index, which has been reported previously in the HH population (2). Among the variables that correlated with poorer NYHA

Table 4. Change in respiratory function following hiatal hernia surgery

	Pre-op	Post-op	*P* value*
Spirometry	*n* = 45	*n* = 45	
FEV_1 – L	2.06 ± 0.67	2.19 ± 0.66	0.003
	2.10 (1.54–2.50)	2.19 (1.70–2.55)	
FEV_1 – % predicted	96 ± 16	105 ± 19	0.0005
	98 (85–107)	102 (95–116)	
FVC – L	2.83 ± 0.88	3.07 ± 0.86	<0.001
	2.72 (2.09–3.55)	3.12 (2.45–3.69)	
FVC – % predicted	107 ± 16	119 ± 19	<0.0001
	108 (93–120)	116 (105–135)	
FEV_1/FVC	73 ± 8	72 ± 6	0.10
FEV_1/FVC – % predicted	97 ± 11	95 ± 9	0.13
	96 (90–103)	95 (89–101)	
$FEF_{25\%–75\%}$ – L	1.62 ± 0.82	1.58 ± 0.74	0.62
	1.40 (0.96–2.22)	1.43 (1.06–2.01)	
$FEF_{25\%–75\%}$ – % predicted	60 ± 26	59 ± 23	0.58
	54 (39–76)	53 (45–69)	
PEF – L/min	5.82 ± 2.04	5.98 ± 1.84	0.15
	5.63 (4.24–6.59)	5.67 (4.69–6.64)	
Peak expiratory flow – % predicted	95 ± 20	99 ± 19	0.08
	93 (82–112)	98 (87–108)	
FEV_1/FVC < 70% – *n* (%)	14/45	16/45	0.75
Reversible airways obstruction – *n* (%)	5/32	3/32	0.69
Lung volumes	*n* = 41	*n* = 41	
TLC – L	4.78 ± 1.09	4.99 ± 1.10	0.0008
	4.54 (3.92–5.47)	4.68 (4.15–5.61)	
TLC – % predicted	93 ± 11	97 ± 10	0.0004
VC – L	2.93 ± 0.87	3.19 ± 0.93	<0.0001
	2.84 (2.12–3.55)	3.10 (2.47–3.78)	
VC – % predicted	105 ± 15	116 ± 18	<0.0001
RV – L	1.86 ± 0.38	1.80 ± 0.34	0.39
	1.85 (1.56–2.15)	1.72 (1.59–1.94)	
RV – % predicted	88 ± 17	86 ± 14	0.26
Expiratory reserve volume – L	0.63 ± 0.39	0.83 ± 0.47	0.001
	0.56 (0.34–0.76)	0.74 (0.47–1.07)	
RV/TLC ratio	39 ± 7	37 ± 6	0.005
	40 (35–44)	36 (32–40)	
TLC < 80% predicted – *n* (%)	4/41	1/41	0.25
RV > 120% predicted – *n* (%)	1/41	0/41	1.0
Airway resistance/conductance	*n* = 30	*n* = 30	
Raw	1.75 ± 0.64	1.72 ± 0.56	0.82
sGaw	0.21 ± 0.05	0.21 ± 0.07	0.80
	0.21 (0.18–0.25)	0.20 (0.16–0.24)	
Diffusing capacity	*n* = 43	*n* = 43	
DLCO – mL/mmHg/min	16.20 ± 4.79	16.39 ± 4.22	0.24
	15.40 (12.60–17.50)	15.50 (13.00–19.50)	
DLCO – % predicted	74 ± 14	76 ± 13	0.19
DLCO/Va – mL/mmHg/min/L	4.25 ± 0.80	3.99 ± 0.70	0.0002
DLCO/Va – % predicted	75 ± 12	71 ± 10	0.0002
DLCO < 70% predicted – *n* (%)	14/43	12/43	0.69
DLCO/Va < 70% predicted – *n* (%)	17/43	17/43	1.0

**P* value for paired *t*-test or Wilcoxon signed-rank test (as indicated) for continuous variables and McNemar test for dichotomous variables.

Table 5. Change in respiratory function stratified by baseline hiatal hernia size

	Group I (ITS ≤ 50%)			Group II (ITS 50%–75%)			Group III (ITS ≥ 75%)		
	Pre-op	Post-op	*P* value	Pre-op	Post-op	*P* value	Pre-op	Post-op	*P* value
Spirometry	*n* = 15	*n* = 15		*n* = 14	*n* = 14		*n* = 16	*n* = 16	
FEV_1 – L	2.01 ± 0.62	2.09 ± 0.61	0.29	2.04 ± 0.48	2.20 ± 0.41	0.054	2.12 ± 0.86 1.92 (1.43–2.52)	2.29 ± 0.86 1.99 (1.68–2.70)	0.03
FEV_1 – % predicted	93 ± 17	98 ± 16	0.20	101 ± 13 100 (94–107)	112 ± 21 105 (99–124)	0.03	95 ± 17	105 ± 17	0.02
FVC – L	2.74 ± 0.81	2.88 ± 0.84	0.15	2.87 ± 0.79	3.16 ± 0.66	0.008	2.86 ± 1.05 2.55 (2.08–3.46)	3.17 ± 1.04 2.79 (2.47–3.72)	0.001
FVC – % predicted	105 ± 15	111 ± 18	0.11	113 ± 15	128 ± 17	0.006	104 ± 18	118 ± 20	0.004
FEV_1 / FVC	73 ± 8 73 (68–80)	73 ± 7 72 (69–74)	0.64	72 ± 8	70 ± 7	0.27	74 ± 8	72 ± 6	0.20
FER – % predicted	96 ± 12 96 (89–105)	96 ± 10 95 (91–97)	0.61	96 ± 10	93 ± 9	0.23	98 ± 11 96 (95–103)	95 ± 7 96 (90–103)	0.35
$FEF_{25\%–75\%}$ – L	1.61 ± 0.75	1.57 ± 0.69	0.73	1.52 ± 0.62	1.48 ± 0.52	0.77	1.71 ± 1.05 1.42 (0.83–2.44)	1.67 ± 0.95 1.32 (0.96–2.08)	0.55
$FEF_{25\%–75\%}$ – % predicted	59 ± 26 58 (38–83)	58 ± 29 52 (44–69)	0.86	59 ± 22	58 ± 19	0.86	61 ± 31 54 (37–76)	59 ± 22 53 (44–72)	0.46
PEF – L/min	5.68 ± 1.93	5.81 ± 1.60	0.56	5.61 ± 1.20	5.73 ± 1.09	0.63	6.12 ± 2.70 5.59 (4.37–6.53)	6.35 ± 2.50 5.61 (4.63–7.41)	0.23
PEF – % predicted	94 ± 23	97 ± 18	0.43	95 ± 16	98 ± 18	0.44	96 ± 22 87 (82–112)	101 ± 21 97 (83–108)	0.15
FEV_1/FVC < 70% – *n* (%)	4/15	5/15	1.0	5/14	5/14	1.0	5/16	6/16	1.0
Reversible airways obstruction – *n* (%)	1/10	2/10	1.0	2/11	1/11	1.0	2/11	0/11	0.50
Lung volumes	*n* = 13	*n* = 13		*n* = 13	*n* = 13		*n* = 15	*n* = 15	
TLC – L	4.73 ± 0.91	4.86 ± 0.99	0.24	4.82 ± 1.16	5.09 ± 1.07	0.002	4.80 ± 1.24 4.41 (3.79–5.78)	5.02 ± 1.28 4.62 (4.14–5.65)	0.054
TLC – % predicted	95 ± 11	98 ± 13	0.15	95 ± 14	101 ± 10	0.007	90 ± 7	94 ± 8	0.058
VC – L	2.94 ± 0.83	3.08 ± 0.88	0.20	2.94 ± 0.75	3.27 ± 0.76	0.009	2.90 ± 1.05 2.64 (1.94–3.53)	3.22 ± 1.15 2.68 (2.46–3.78)	0.003
VC – % predicted	104 ± 14	110 ± 20	0.09	111 ± 16	125 ± 18	0.005	101 ± 13	114 ± 14	0.002
RV – L	1.79 ± 0.31	1.78 ± 0.21	0.94	1.88 ± 0.51	1.83 ± 0.44	0.59	1.90 ± 0.30	1.80 ± 0.35	0.21
RV – % predicted	92 ± 21	91 ± 13	0.85	87 ± 19	85 ± 16	0.59	87 ± 8	82 ± 14	0.18
Expiratory reserve volume – L	0.54 ± 0.42 0.40 (0.29–0.66)	0.71 ± 0.36 0.65 (0.47–0.86)	0.07	0.75 ± 0.41 0.60 (0.49–0.92)	0.98 ± 0.44 1.04 (0.63–1.14)	0.13	0.60 ± 0.34	0.81 ± 0.56	0.04
RV/TLC ratio	38 ± 8	38 ± 6	0.62	39 ± 5 40 (37–40)	36 ± 5 38 (32–40)	0.24	41 ± 7	37 ± 8	0.003
TLC < 80% predicted – *n* (%)	1/13	1/13	1.0	2/13	0/13	0.50	1/15	0/15	1.0
RV > 120% predicted – *n* (%)	1/13	0/13	1.0	0/13	0/13	–	0/15	0/15	–
Airway resistance/conductance	*n* = 9	*n* = 9		*n* = 12	*n* = 12		*n* = 9	*n* = 9	
Raw	1.87 ± 0.75	1.86 ± 0.66	0.98	1.71 ± 0.58	1.90 ± 0.48	0.37	1.69 ± 0.66	1.35 ± 0.38	0.048
sGaw	0.21 ± 0.06 0.23 (0.18–0.26)	0.20 ± 0.08 0.20 (0.14–0.24)	0.57	0.20 ± 0.03	0.18 ± 0.04	0.29	0.23 ± 0.08	0.25 ± 0.07	0.07
Diffusing capacity	*n* = 14	*n* = 14		*n* = 13	*n* = 13		*n* = 16	*n* = 16	
DLCO – mL/mmHg/min	16.89 ± 3.89	17.06 ± 3.31	0.68	14.65 ± 3.53	14.97 ± 3.72	0.44	16.87 ± 6.19 14.60 (12.45–20.85)	16.96 ± 5.18 15.40 (12.28–21.70)	0.54
DLco – % predicted	77 ± 11	78 ± 10	0.46	71 ± 16	73 ± 16	0.35	75 ± 14	77 ± 13	0.52
DLCO/Va – mL/mmHg/min/L	4.58 ± 0.72 4.77 (4.18–4.95)	4.27 ± 0.57 4.33 (3.96–4.68)	0.005	3.91 ± 0.87	3.69 ± 0.64	0.06	4.24 ± 0.74	4.00 ± 0.77	0.07
DLco/Va – % predicted	79 ± 10	73 ± 7	0.003	70 ± 13	66 ± 10	0.08	76 ± 13	72 ± 13	0.07
DLco < 70% predicted – *n* (%)	3/14	2/14	1.0	6/13	6/13	1.0	5/16	4/16	1.0
DLco/Va < 70% predicted – *n* (%)	3/14	3/14	1.0	7/13	7/13	1.0	7/16	7/16	1.0

P values for paired *t*-test or Wilcoxon signed-rank test (as indicated) for continuous variables or McNemar test for dichotomous variables.

classification, TLC, RV/TLC ratio and FEV_1 all improved post-operatively, indicating that these parameters were abnormal because of the space-occupying effect of the hernia. However, the magnitude of increase in these respiratory parameters post-operatively was modest. This may be partly explained by post-operative RFT being performed at short-term follow-up (median of ~3 months); however, the clinical relevance of further improvements in RFT beyond this time point is uncertain given that NYHA class had already improved markedly. HH recurrence may also contribute to the modest improvement in RFT following surgery; however, our group has recently demonstrated very low rates (only 2%) of symptomatic HH recurrence at 3–6 months and low rates (7%) of asymptomatic recurrences, with all asymptomatic recurrences representing small hernias (29). While this may account for a lack of improvement in a small number of patients, recurrence of a small HH is unlikely to have a significant impact on RFT because of a space-occupying effect.

The overall modest improvement in RFT parameters post-operatively and, moreover, the observation of normal mean pre-operative values despite severe NYHA functional impairment suggests that while respiratory dysfunction may contribute to symptoms in HH patients, other pathophysiological mechanisms may be more important. For example, we have previously demonstrated a correlation between the magnitude of resolution of HH-related left atrial compression and exercise capacity improvement that is independent of the resolution in respiratory parameters (7). Additionally, diaphragmatic dysfunction has also been suggested by some authors (3) although there are few data correlating this with patient symptoms.

Study limitations

The primary limitation of this study is selection bias as we primarily included patients with large HH that proceeded to surgical repair, limiting the clinical applicability of our results to similar patients. Second, many patients did not present for post-operative RFT. However, there was no statistically significant difference in baseline NYHA functional class between patients who did undergo post-operative RFT compared with patients who did not undergo post-operative RFT (data not shown), limiting the risk of misinterpretation of the effect of surgery. Third, RFT evaluation was undertaken under standard conditions without oral loading similar to prior studies (2, 3) and to permit comparisons using established normative data. Prior studies evaluating RFT 2 h following a meal showed no change in spirometry, lung volumes or DLCO among both healthy patients and patients with

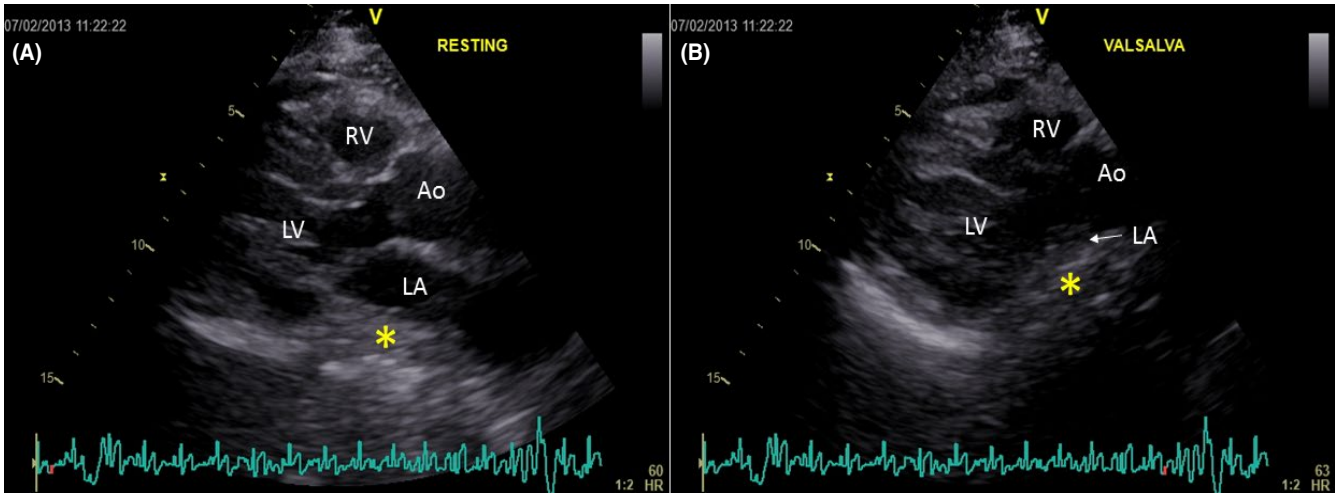


FIGURE 1 Two-dimensional echocardiograms demonstrating mild LA compression at rest (A) by a hiatal hernia (*) and severe LA compression during Valsalva maneuver (B) in the same patient. LA=left atrium; LV=left ventricle; RV=right ventricle; Ao=aorta

patients, further preload reduction induced by VM may overwhelm compensatory mechanisms responsible for preserving LV filling under resting conditions. One prior case report has demonstrated encroachment of the LA during VM in a patient with a large HH,[5] and we have noted several cases of significant LA compression induced by VM in patients with large HH and only mild resting LA compression (Figure 1). To the best of our knowledge, the effects of VM on HH-induced LA compression and LV filling have never been systematically studied.

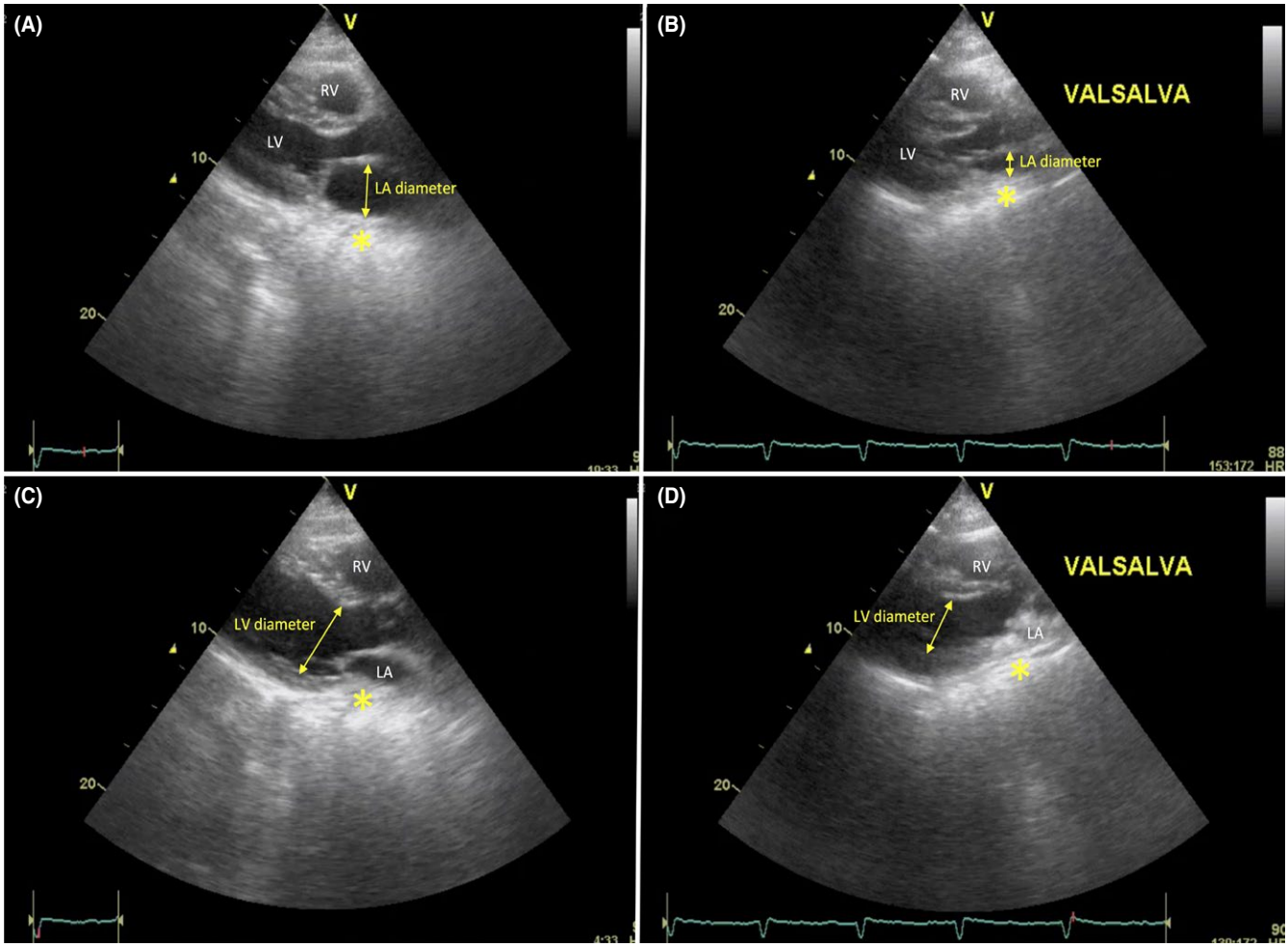


FIGURE 2 Two-dimensional echocardiograms demonstrating measurement of LA (A and B) and LV diameters (C and D) at rest (A and C) and during Valsalva maneuver (B and D). *denotes hiatal hernia. LA=left atrium; LV=left ventricle; RV=right ventricle

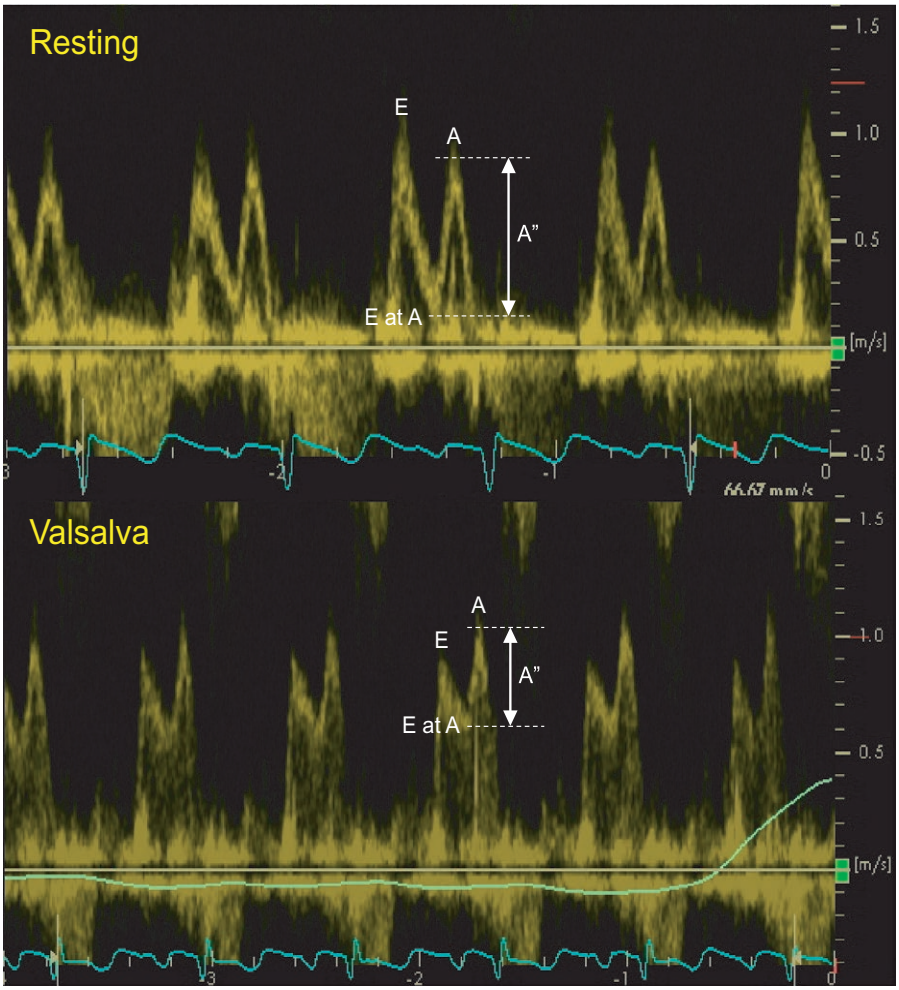


FIGURE 3 Measurement of mitral inflow Doppler during Valsalva maneuver. Peak mitral A velocity was corrected for the E velocity at A-wave onset. A′′=corrected peak A velocity

We, therefore, conducted an echocardiographic evaluation of the effect of VM on LA and LV filling and other cardiac parameters in HH patients and in age- and sex-matched controls.

2 | METHODS

2.1 | Study populations

Consecutive patients with large HH referred to an outpatient cardiology clinic for clinical evaluation prior to plan HH surgery between March 2012 and February 2014 were included as study (HH) patients. The effect of VM on LA and LV chamber dimensions and LV filling indices was compared between study(HH) patients and a control group. Clinical evaluation of all patients was performed at baseline including assessment of patient demographics, New York Heart Association Class and comorbidities. The Institutional Human Research Ethics Committee approved the study and all patients provided written informed consent.

Age- and sex-matched control patients were identified from two outpatient clinics. For this group, patients with cardiac or respiratory comorbidities were excluded if they had any one of the following exclusion criteria: reduced LV systolic function (LVEF<50%), known myocardial ischemia, congestive heart failure, severe valvular or hypertrophic heart disease, and/or clinically severe pulmonary disease. Patients with a permanent pacemaker or history of atrial fibrillation were excluded if not in sinus rhythm at the time of echocardiographic assessment. Only patients with a known large HH were excluded from the control group given the high prevalence of small sliding hiatal hernia in this age group (60% in patients over 50 years).[6]

2.2 | Transthoracic echocardiography

Transthoracic echocardiography was performed with the patient in the left lateral position using a Vivid-9 GE cardiac ultrasound (Vingmed, GE, Horten, Norway). Studies were digitally recorded and analyzed offline in batches by a single observer (CN). Conventional echocardiographic parameters were measured in study and control subjects at rest according to American Society of Echocardiography guidelines.[7] HH patients were instructed to consume a meal prior to presenting for clinical evaluation to distend the hernia.

Patients were instructed to perform VM in a recumbent position for up to approximately 10 seconds,[8] and measurements were performed during separate repeated maneuvers. Trained operators instructed the patients on how to perform VM and meticulous attention was given to ensuring patients executed a satisfactory maneuver. Measurements performed during the strain phase included the following: maximal anteroposterior LA and diastolic LV diameter in the parasternal long-axis view (Figure 2); diastolic apical two- and four-chamber LV volumes using modified Simpson's method (average of two- and four-chamber volumes are reported); and transmitral E- and A-wave diastolic

TABLE 1 Clinical and Doppler echocardiographic characteristics at rest

	Controls N=22	HH patients N=55	*P*-value
Demographics			
Age – y	67±6	70±10	.24
Female gender – no.	13/22 (59%)	43/55 (78%)	.08
Systolic blood pressure – mm Hg	136±6 135 (135–136)	141±12 140 (135–145)	.01
Body mass index – kg/m^2	27.9±4.6	30.7±5.0	.02
Clinical comorbidities			
Hypertension	14/22	37/55	.76
Diabetes	3/22	5/55	.55
Dyslipidemia	10/22	34/55	.19
Smoking history	8/22	18/55	.76
Cardiac comorbidities – no.[a]	8/22	12/55	.19
Respiratory comorbidities – no.[b]	8/22	24/55	.56
Echocardiographic parameters			
LA diameter/BSA – mm/m^2	19±2	16±5	.01
LV diastolic diameter/BSA – mm/m^2	22±3	21±3	.34
LV systolic diameter/BSA – mm/m^2	14±2	13±3	.06
Average wall thickness/BSA – mm/m^2	5.0±0.7 5.0 (5.0–5.3)	5.8±1.2 6.0 (5.0–6.0)	.008
Fractional shortening – %	37±7	42±10	.06
LV diastolic volume/BSA – mL/m^2	38±8 37 (34–41)	32±9 30 (24–37)	.001
LV systolic volume/BSA – mL/m^2	13±4 14 (11–16)	11±5 10 (7–13)	.01
LV stroke volume/BSA – mL/m^2	25±6 25 (21–27)	21±6 20 (16–25)	.006
LV ejection fraction – %	65±6	66±8	.52
LV diastolic mass/BSA – g/m^2	75±18	71±15	.31
RV outflow tract diameter/BSA – mm/m^2	18±2	16±3	.005
RV systolic pressure – mm Hg	27±4	33±7	.004
S-wave – cm/s	64±10 64 (53–72)	79±19 75 (66–93)	.0003
D-wave – cm/s	43±9 42 (34–48)	54±15 51 (44–62)	.0008
S/D ratio	1.53±0.30 1.52 (1.32–1.71)	1.53±0.37 1.48 (1.25–1.72)	.64
E-wave – cm/s	70±10	75±18	.18
A-wave – cm/s	77±17	83±17	.17
E/A ratio	0.95±0.27 0.95 (0.72–1.07)	0.91±0.17 0.93 (0.80–1.02)	.83
DT – ms	211±47 205 (176–225)	207±41 200 (183–233)	.96
E/e′	11.8±2.7 11.8 (10.9–12.9)	12.7±3.6 12.1 (10.3–15.3)	.32
LVOT stroke volume/BSA – mL/m^2	48±10	43±9	.052
Cardiac index – L/min	3.18±0.86 3.24 (2.48–3.81)	3.21±0.71 3.31 (2.58–3.73)	.64

[a]Cardiac disease: CAD, CHF, atrial arrhythmia, moderate or greater valvular disease.
[b]Respiratory disease: COPD, asthma, PE, OSA, other lung disease.

TABLE 2 Left atrial and ventricular dimensions at rest and during VM

	Control patients N=22	HH patients N=55	*P*-value[b]
LA diameter/BSA – mm/m^2			
Rest	19±2	16±5	.009
Valsalva	16±3	9±5	<.0001
Δ – mean (SD)	−3 (2)	−7 (4)	.0001
Δ – %	−16%	−42%	<.0001
P-value[a]	<.0001	<.0001	
LV diastolic diameter/BSA – mm/m^2			
Rest	22±3	21±3	.34
Valsalva	19±3	17±3	.01
Δ – mean (SD)	−3 (2)	−4 (3)	.06
Δ – %	−12%	−19%	.054
P-value[a]	<.0001	<.0001	
Heart rate – bpm			
Rest	68±10	75±9	.0007
Valsalva	74±15	81±13	.03
Δ – mean (SD)	+8 (7)	+7 (8)	.60
sΔ – %	+11%	+9%	.40
P-value[a]	<.0001	<.0001	
LV diastolic volume/ BSA – mL/m^2	N=21	N=39	
Rest	38±8	31±8	.002
	36 (34–42)	31 (24–37)	
Valsalva	26±10	19±9	.005
Δ – mean (SD)	−12 (8)	−12 (7)	.99
Δ – %	−32%	−40%	.16
P-value[a]	<.0001	<.0001	

P-value for paired comparison between rest and Valsalva (a) and unpaired comparison between hiatal hernia and control groups (b).

velocities and E-wave DT in the four-chamber view. LA and LV dimensions were obtained during a single VM from a parasternal long-axis view; two-chamber and four-chamber LV volumes and mitral inflow were obtained during three separate VM from an apical window. To correct for E/A fusion during VM as a result of relative tachycardia, E-wave velocity was also measured at the onset of the A-wave, and absolute A-wave velocity (A″) was calculated as previously described (A″= [A-wave velocity]—[E-wave velocity at A-wave onset])[9] and depicted in Figure 3.

2.3 | Statistical analysis

Continuous data are presented as mean ± SD. Paired analyzes between resting and Valsalva data were performed using a paired *t* test or Wilcoxon matched pairs test as appropriate. Comparisons between study and control patients were performed using an unpaired *t* test or Mann–Whitney test for continuous data; and chi-square test or chi-square test for trend for categorical variables, as appropriate. The degree of resting LA compression was graded qualitatively (none, mild, moderate, and severe) as previously described,[1] and HH patients were further stratified during analysis into two groups based on their resting LA compression grade ("none-mild" vs "moderate-severe"). Changes in Doppler-echocardiographic parameters during VM were compared among HH subgroups and controls using an ordinary one-way ANOVA or Kruskal–Wallis test as appropriate. Tukey's or Dunn's multiple comparisons tests were performed to further delineate differences between groups.

3 | RESULTS

Between March 2012 and February 2014, 55 of 62 (89%) consecutively evaluated HH patients had assessment of LA and LV dimensions at rest and during VM. Adequate echocardiographic data to accurately assess LA and LV 2D dimensions during VM were not obtained in seven patients who were excluded. LA and LV dimensions were obtained in all patients (n=55) at rest and during VM. Due to the intensive nature of the study protocol including the need for repeated VM as well as the technical difficulties associated with obtaining apical transthoracic imaging during VM, LV volumes (n=39) and mitral inflow parameters (n=27) could only be obtained in a subpopulation of the study patients. Twenty-two control patients were identified between March 2014 and June 2014 and underwent assessment during VM for comparison.

Baseline characteristics for study patients and controls are presented in Table 1. HH patients had higher BMI and resting systolic blood pressure levels than controls; however, there were no significant differences in the prevalence of other comorbidities between the two groups. LA and RV dimensions and LV volumes were smaller in HH patients compared with controls, and systolic and diastolic LA inflow velocities and RVSP were higher in HH patients. There were no differences in LV filling indices, including E/e' ratio, between groups at baseline.

VM resulted in a significant increase in heart rate and reduction of maximal LA and LV diameters and LV diastolic volume in both HH patients and controls (Table 2).The reduction in LA diameter during VM was significantly greater in HH patients than in controls (−42% vs −16%, *P*<.0001). Resting LA diameter was similar in control and HH patients with none-mild resting LA compression, but was significantly decreased in patients with moderate-severe resting LA compression (19±2 mm/m^2 controls, 20±2 mm/m^2 HH none-mild, 14±4 mm/m^{2}HH moderate-severe; *P*<.001 for ANOVA, *P*=.42 for posttest comparison between controls and none-mild LA compression and *P*<.0001 for all other comparisons). However, during VM, LA diameter was significantly lower in all HH patients compared to controls, even among patients with only none-mild resting LA compression (16±3 mm/m^2 controls, 12±5 mm/m^2 HH none-mild, 7±3 mm/m^2 HH moderate-severe; *P*<.0001 for ANOVA and *P*<.01 for all posttest comparisons; Figure 4). Patients with moderate-severe LA compression at rest developed even more profound LA compression during VM (Figure 4). The percent reduction in LA diameter with VM was significantly

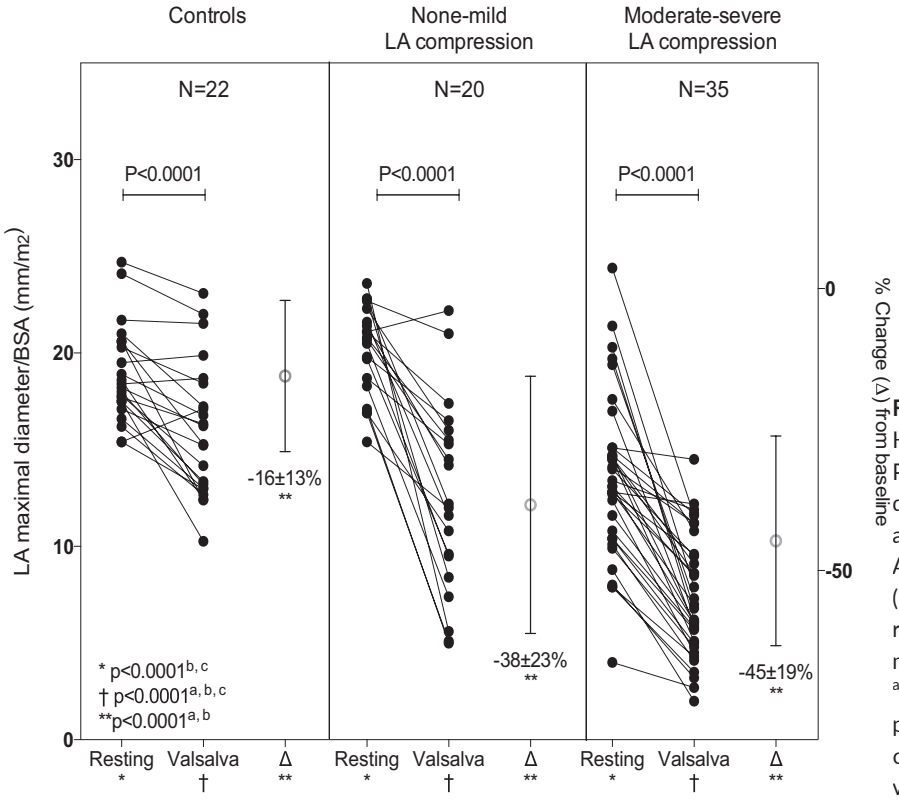


FIGURE 4 Change in LA diameter in HH patients stratified by LA compression. Paired *t* test values are shown for differences in LA diameter between rest and VM within each group. *P*-values for ANOVA inter-group comparison at rest (*), during VM (†) and for the percent reduction in LA diameter (**). Posttest multiple comparisons *P*-value <.01 for [a]controls vs none-mild LA compression patients; [b]controls vs moderate-severe LA compression; [c]none-mild LA compression vs moderate-severe LA compression

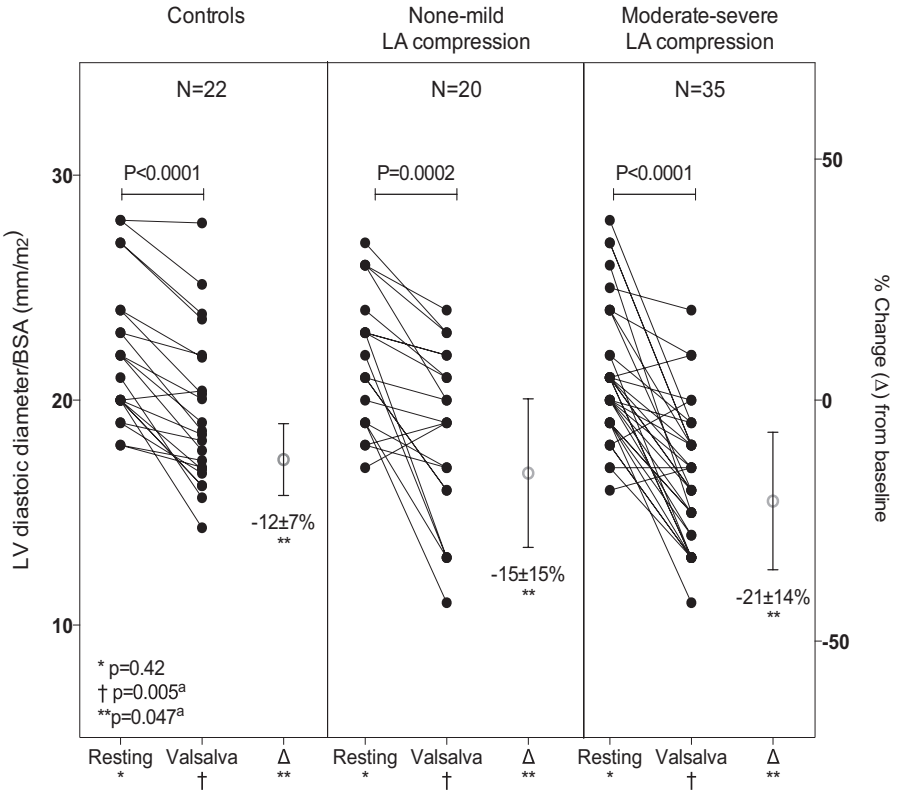


FIGURE 5 Change in LV diastolic diameter in HH patients stratified by severity of resting LA compression. Paired *t* test values are shown for differences in LV diameter between rest and VM within each group. *P*-values for ANOVA or Kruskal–Wallis (as appropriate) inter-group comparison at rest (*), during VM (†) and for the percent reduction in LV diameter (**). Posttest multiple comparisons *P*-value <.05 for [a]controls vs moderate-severe LA compression patients

greater in HH patients with none-mild LA compression compared to controls (−38±23% vs −16±13%, *P*=.0003). Put together, these data indicate that VM can unmask severe LA compression in HH patients with apparently mild resting LA compression.

Changes in LV dimensions during VM are also presented in Table 2. VM resulted in a significant reduction in LV diameter in controls and HH patients (*P*<.001 for both). Interestingly, mean LV diastolic diameter was not significantly different between HH patients and controls at rest (22±3 mm/m^2 vs 21±3 mm/m^2, *P*=.34); however during VM, LV diameter was significantly less in HH patients than in controls (17±3 mm/m^2 vs 19±3 mm/m^2, *P*=.01) suggesting that VM may induce a relatively greater reduction in LV filling in HH patients. Moreover, while the percent reduction in LV diameter only trended to being greater in HH patients compared with controls (−19% vs −12%, *P*=.054), there was a

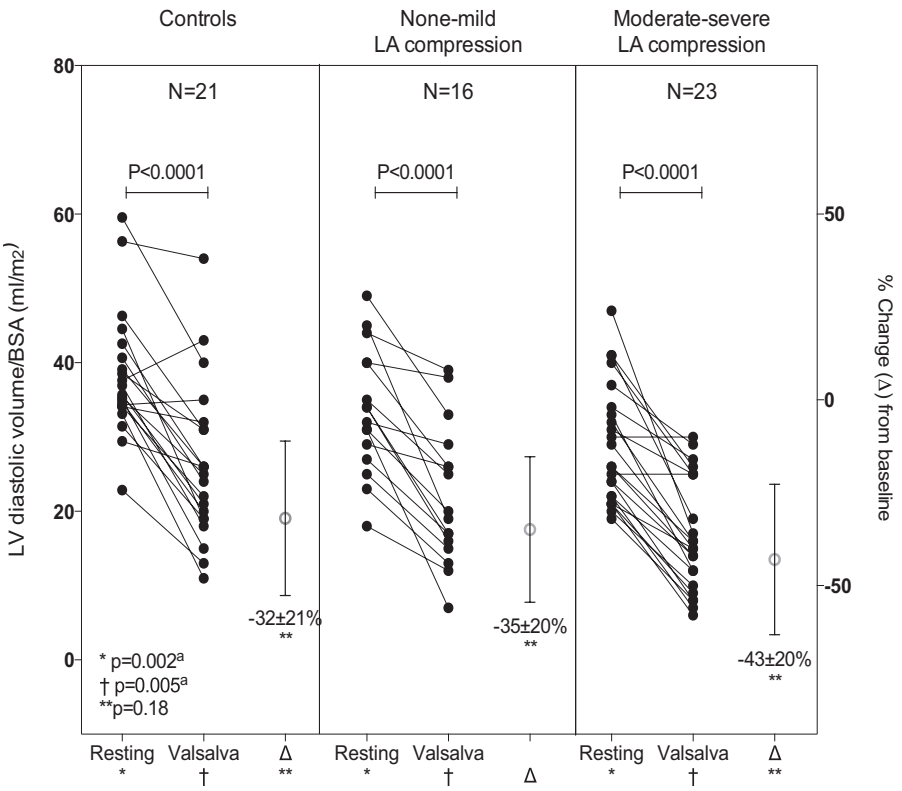


FIGURE 6 Change in LV diastolic volume in HH patients stratified by severity of resting LA compression. Paired *t* test *P*-values are shown for differences in LV volume between rest and VM within each group. *P*-values for ANOVA or Kruskal–Wallis (as appropriate) inter-group comparison at rest (*), during VM (†) and for the percent reduction in LV diameter (**). Posttest multiple comparisons *P*-value <.05 for [a]controls vs moderate-severe LA compression patients

significant difference when HH patients were stratified according to the severity of LA compression at rest (controls −12%, HH with none-mild LA compression −15%, and HH with moderate-severe LA compression, −21%, ANOVA *P*=.047; Figure 5). Post-ANOVA tests showed that this result was only significant for the comparison between controls and HH patients with moderate-severe LA compression.

LV diastolic volume decreased significantly during VM in controls and HH patients (Table 2). Although LV volumes were decreased in HH patients compared with controls at rest (31±8 mL/m^2 vs 38±8 mL/m^2, *P*=.002) and during VM (19±9 mL/m^2 vs 26±10 mL/m^2, *P*=.005), the proportional reduction in LV diastolic volume during VM was not significantly different between groups (−32% in controls vs −40% in HH patients, *P*=.16). There was a trend to a greater percent reduction in LV diastolic volume in the moderate-severe LA compression group compared with none-mild HH patients and controls; however, this was not statistically significant (Figure 6).

VM significantly reduced mitral E velocity by 20% or more in both controls and HH patients (*P*<.001, Table 3). However, mitral inflow parameters were not significantly different when comparing HH patients and controls, either at rest or during VM (Table 3). The mitral A velocity only decreased significantly in controls with VM, however, A″ decreased in both groups. Mean E/A ratio decreased similarly in both groups, however, after correcting for heart rate response and E/A fusion during VM, there was no significant reduction in E/A″ ratio in either group. The increase in E-wave DT during VM was significant in controls and borderline significant in HH patients.

Interestingly, the LA diameter during VM, a surrogate measure of LA compression severity, correlated inversely with E velocity during VM in HH patients (*R*=−.43, *P*=.03) but not controls (*R*=.18, *P*=.43). LA diameter during VM correlated positively with mitral A velocity during VM in control patients (*R*=.57, *P*=.005) but not in HH patients (*R*=.32, *P*=.10) (Figure 7).

4 | DISCUSSION

This is the first systematic Doppler-echocardiographic study to evaluate the functional effects of VM on cardiac hemodynamics in patients with large HH. We have demonstrated that VM causes severe LA compression in patients with only mild resting LA compression. HH patients with more severe LA compression also demonstrated significantly greater reduction in LV diameter than controls during VM, suggesting an important interaction between the severity of HH-mediated LA compression, preload reduction and compromised LV filling. LA compression during VM appears to be associated with higher early diastolic (E) filling velocities, which may contribute to the relative preservation of LV volumes in HH patients.

In HH patients, VM resulted in a 42% reduction in LA diameter compared to 16% in control patients. Moreover, among HH patients with none or only mild resting LA compression, a marked reduction of LA diameter was observed during VM (Figure 4). Early echocardiographic studies demonstrated a 30% decrease in LA diameter in healthy controls during VM and a significantly blunted hemodynamic response (approximately 4%) in patients with cardiovascular disease and NYHA class III or IV symptoms[4] reflecting elevated LA pressure. Worsening LA compression by a HH during VM has only been demonstrated in one single prior report.[10] Increased LA compression with VM may be related to increased abdominal pressure increasing intrathoracic protrusion of the hernia. This possibility is supported by the established diagnostic

TABLE 3 Mitral inflow characteristics during VM

	Control patients N=22	HH patients N=27	*P*-value[b]
Mitral valve inflow			
E-wave – cm/s			
Rest	70±10	73±19	.46
Valsalva	53±13	57±16	.41
Δ – mean (SD)	−16 (12)	−16 (14)	.97
Δ – %	−23%	−20%	.64
P-value[a]	<.0001	<.0001	
A-wave – cm/s			
Rest	77±17	82±18	.35
Valsalva	71±20	79±23	.22
Δ – mean (SD)	−6 (13)	−3 (17)	.50
Δ – %	−7%	−3%	.44
P-value[a]	.048	.38	
E/A ratio			
Rest	0.95±0.27	0.89±0.16	.41
Valsalva	0.80±0.31	0.73±0.12	.93
	0.75 (0.57–1.07)	0.71 (0.67–0.82)	
Δ – mean (SD)	−0.14 (0.28)	−0.16 (0.17)	.95
Δ – %	−13%	−16%	.85
P-value[a]	.01	<.0001	
DT – ms			
Rest	211±47	204±42	.98
	205 (176–225)	206 (178–225)	
Valsalva	259±72	240±94	.47
Δ – mean (SD)	+45 (74)	+32 (87)	.59
Δ – %	+24%	+17%	.57
P-value[a]	.01	.07	
A″ – cm/s			
Rest	73±17	65±19s	.13
	70 (64–84)	64 (51–70)	
Valsalva	56±25	55±15	.81
Δ – mean (SD)	−17 (20)	−10 (20)	.25
Δ – %	−23%	−11%	.16
P-value[a]	.0006	.02	
E/A″			
Rest	1.00±0.28	1.18±0.43	.18
Valsalva	1.38±1.52	1.10±0.41	.47
	0.95 (0.66–1.27)	0.96 (0.82–1.26)	
Δ – mean (SD)	+0.38 (1.45)	−0.09 (0.54)	.55
Δ – %	+36%	−1%	.62
P-value[a]	>.99	.40	

P-value for paired comparison between rest and Valsalva values ([a]) and unpaired comparison between hiatal hernia and control groups ([b]). Nonparametric or parametric test used as appropriate.

utility of VM in identifying both GOR and HH during radiological examinations.[11] A second possibility is that the reduction of LA pressure due to reduced venous return during the strain phase of Valsalva may render the LA more susceptible to extrinsic compression by HH.

LV diameter was also significantly decreased in HH patients compared to controls during VM despite no difference observed between groups at rest. VM may decrease LV diameter by increasing the degree of intra-thoracic protrusion of the hernia leading to increased direct LV compression (as reported previously,[12])and/or decreasing LV filling via the reduction in venous return from the systemic circulation and via the compression of the LA. In a prior study, during VM LV diameter was decreased by 11% in healthy controls,[4] which is similar to the magnitude of change observed in our control patients. A diminished response has been observed in patients with heart failure and reduced LV systolic function.[13]

Although LA filling and anteroposterior LV diameter were both decreased during VM, the overall effect on LV volumes was relatively mild with no difference observed in the reduction of LV diastolic volume during VM between HH patients and controls. We have shown that under resting conditions HH-related LA compression results in reduced LA filling (LAV_{Max}) with minimal affect on LV filling through modulation of LA emptying function.[2] The changes in mitral Doppler velocities during VM in the present study may explain the relative preservation of LV volume despite significantly reduced LA filling. In healthy patients, preload reduction induced by VM causes a relatively proportional reduction in both E and A velocity with no significant change of the E/A ratio.[14] Reduced E and A velocities have been verified in animal studies of sudden preload reduction induced by inferior vena cava occlusion.[15] A more unique finding to the HH patients was the observation that LA diameter during VM correlated inversely with early diastolic filling velocity (E), suggesting that the more severe the LA compression the greater the early diastolic filling velocity during VM. Augmented early diastolic filling to preserve LV volume has been previously observed in animal studies of isolated atrial tamponade [16] and may therefore be present under conditions of reduced preload in patients with HH subjected to VM.

5 | STUDY LIMITATIONS

First, the cohort study only included patients with large HH being considered for surgery, limiting our observations to similar patients. Second, VM was not performed using a Valsalvometer which has been shown to effectively minimize the variation of abdominal pressure generated by VM.[17] However, patients were instructed to perform VM by the same operators and with similar instructions and our data therefore reflect the hemodynamic effect expected to occur by a routine clinical VM performed in daily practice. Moreover, the tachycardia and Doppler echocardiographic changes observed in the controls during VM are consistent with previously reported responses.[9] Third, we did not perform assessment of mitral annular tissue Doppler, which may have provided additional information

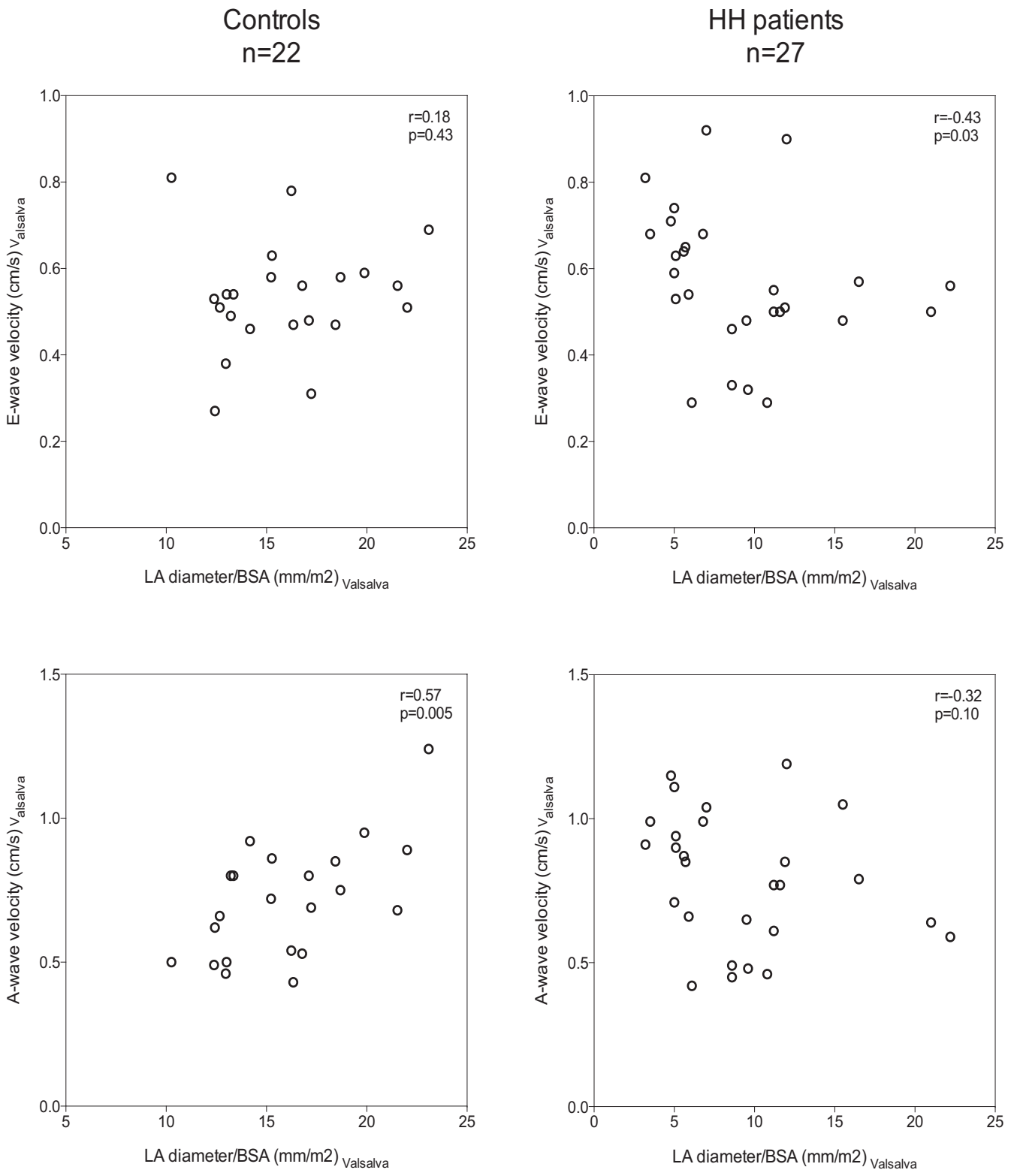


FIGURE 7 Spearman correlation between maximal LA diameter index and LV filling indices during Valsalva maneuver

regarding diastolic function. Finally, standardized feeding was not performed prior to Doppler-echocardiographic assessment. Feeding results in short-lived changes to commonly measured Doppler-echocardiographic parameters in healthy subjects.[18] Further studies are needed to assess the time-dependent impact of feeding on Doppler-echocardiographic parameters in HH patients and the additional impact of VM in this setting.

6 | CONCLUSIONS

This is the first study evaluating the physiological impact of VM on cardiac filling and hemodynamics in HH patients. LA filling is more significantly decreased by VM in HH patients than in controls. LA compression during VM appears to be associated with higher early diastolic filling velocities, which may contribute to the relative preservation of LV volumes under

these conditions. These findings improve our understanding of the contribution of LA function to overall cardiovascular performance in this cohort.

ACKNOWLEDGMENTS

The authors would like to thank Diana Hanzek and Zoya Pogrebizhsky for their assistance in performing the cardiac ultrasound studies.

REFERENCES

1. Naoum C, Falk GL, Ng AC, et al. Left atrial compression and the mechanism of exercise impairment in patients with a large hiatal hernia. *J Am Coll Cardiol*. 2011;58:1624–1634.
2. Naoum C, Kritharides L, Thomas L, et al. Modulation of phasic left atrial function and left ventricular filling in patients with extrinsic left atrial compression by hiatal hernia. *Int J Cardiol*. 2014;176:1176–1178.
3. Nishimura RA, Tajik AJ. The Valsalva maneuver-3 centuries later. *Mayo Clin Proc*. 2004;79:577–578.
4. Robertson D, Stevens RM, Friesinger GC, Oates JA. The effect of the Valsalva maneuver on echocardiographic dimensions in man. *Circulation*. 1977;55:596–602.
5. Buss S, Katus HA, Mereles D. Dynamic changing mass behind the left atrium. *Heart*. 2007;93:1583.
6. Hyun JJ, Bak YT. Clinical significance of hiatal hernia. *Gut Liv*. 2011;5:267–277.
7. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18:1440–1463.
8. Opotowsky AR, Ojeda J, Rogers F, Arkles J, Liu T, Forfia PR. Blood pressure response to the valsalva maneuver. A simple bedside test to determine the hemodynamic basis of pulmonary hypertension. *J Am Coll Cardiol*. 2010;56:1352–1353.
9. Hurrell DG, Nishimura RA, Ilstrup DM, Appleton CP. Utility of preload alteration in assessment of left ventricular filling pressure by Doppler echocardiography: a simultaneous catheterization and Doppler echocardiographic study. *J Am Coll Cardiol*. 1997;30:459–467.
10. Buss S, Katus HA, Mereles D. Dynamic changing mass behind the left atrium. *BMJ Case Rep*. 2009;2009:bcr2006107136.
11. Izbicki JRBD, Yekebas EF. *Surgery of the Esophagus: Textbook and Atlas of Surgical Practice*. Germany: Springer Science & Business Media; 2009.
12. D'Cruz IA, Hancock HL. Echocardiographic characteristics of diaphragmatic hiatus hernia. *Am J Cardiol*. 1995;75:308–310.
13. Parisi AF, Harrington JJ, Askenazi J, Pratt RC, McIntyre KM. Echocardiographic evaluation of the Valsalva Maneuver in healthy subjects and patients with and without heart failure. *Circulation*. 1976;54:921–927.
14. Dumesnil JG, Gaudreault G, Honos GN, Kingma JG Jr. Use of Valsalva maneuver to unmask left ventricular diastolic function abnormalities by Doppler echocardiography in patients with coronary artery disease or systemic hypertension. *Am J Cardiol*. 1991;68:515–519.
15. Courtois M, Vered Z, Barzilai B, Ricciotti NA, Perez JE, Ludbrook PA. The transmitral pressure-flow velocity relation. Effect of abrupt preload reduction. *Circulation*. 1988;78:1459–1468.
16. Fowler NO, Gabel M. Regional cardiac tamponade: a hemodynamic study. *J Am Coll Cardiol*. 1987;10:164–169.
17. Greenland HP, Hosker GL, Smith AR. A valsalvometer can be effective in standardising the Valsalva manoeuvre. *Int Urogynecol J Pelvic Floor Dysfunct*. 2007;18:499–502.
18. Dencker M, Bjorgell O, Hlebowicz J. Effect of food intake on commonly used pulsed Doppler and tissue Doppler measurements. *Echocardiography*. 2011;28:843–847.

How to cite this article: Naoum C, Kritharides L, Gnanenthiran SR, Martin D, Falk GL, Yiannikas J. Valsalva maneuver exacerbates left atrial compression in patients with large hiatal hernia. *Echocardiography*. 2017;34:1305–1314. https://doi.org/10.1111/echo.13628

International Journal of Cardiology 182 (2015) 291–293

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Letter to the Editor

Postprandial left atrial filling is impaired in patients with large hiatal hernia and improves following surgical repair☆

Christopher Naoum [a], Rajesh Puranik [b], Gregory L. Falk [c], John Yiannikas [a], Leonard Kritharides [a,*]

[a] Department of Cardiology, Concord Hospital, Sydney Medical School, The University of Sydney, Sydney, Hospital Road, Concord, NSW 2139, Australia
[b] Department of Cardiology, Royal Prince Alfred Hospital, Sydney Medical School, The University of Sydney, Sydney, Missenden Road, Camperdown, NSW 2050, Australia
[c] Department of Upper Gastrointestinal Surgery, Concord Hospital, Sydney Medical School, The University of Sydney, Sydney, Hospital Road, Concord, NSW 2139, Australia

ARTICLE INFO

Article history:
Received 10 December 2014
Accepted 29 December 2014
Available online 31 December 2014

Keywords:
Hiatal hernia
Left atrial compression
Cardiac compression
Left atrial filling
Postprandial haemodynamics

Left atrial (LA) compression is common in patients with large hiatal hernia (HH) [1]. The observation of postprandial cardiac symptoms in this population as well as hemodynamic instability due to acute gastroparesis following thoraco-abdominal surgery suggests that increased cardiac compression due to acute hernia distension may be hemodynamically important [2,3]. However, there are few data regarding these effects with a prior study of two HH patients, demonstrating variable effects of a meal on stroke volume [4]. Cardiac MRI (CMR) allows reliable calculation of cardiac volumes, while simultaneously permitting estimation of HH volume before and after feeding. We accordingly performed a CMR study to assess the acute effects of feeding on hernia volume and cardiac parameters in patients with clinically significant HH.

Ten patients (mean ± SD age, 66 ± 8 years; 6 female) with large HH (baseline characteristics in Supplementary table) underwent CMR before and after standardized oral feeding (2–3 servings × 140–150 g rice-pudding, PDP Fine Foods, Bankstown, NSW or LD&D Foods, Docklands, Victoria; followed by 5–10 ml/kg mannitol). Five patients were evaluated following corrective HH surgery for comparison (4 of whom were evaluated pre-operatively). The Institutional Ethics Committee approved the study and all patients provided written informed consent.

CMR was performed on a 1.5 T scanner (Achieva, Philips Medical Systems) and volumetric analyses using Osirix Dicom Viewer. Axial thoraco-abdominal survey images were used to estimate hernia volume by disc summation. Steady-state free precession short-axis cine images of the ventricles were acquired during held-respiration (repetition time (TR) = 4–6 ms; echo time (TE) = 1.6–3.0 ms; flip angle = 60°; slice thickness = 10 mm; matrix = 192 × 256; field of view = 340–360 mm) for calculation of ventricular volumes. Short-axis imaging of the LA was similarly acquired (TR = 4–6 ms; TE = 1.6–3 ms; flip angle = 60°; slice thickness = 8 mm; matrix = 192 × 256; field of view = 340–360 mm). The LA endocardial border was manually traced in contiguous slices at each phase of the cardiac cycle, excluding the LA appendage and pulmonary veins. Maximal (LAV_{Max}), minimal (LAV_{Min}) and pre-atrial systole (LAV_{PreA}) volumes were identified by reviewing the multiphasic data. Area under the multiphasic LA volume curve (AUC) was calculated as the sum of the phasic LA volume × phase duration product for each phase $\left(\text{AUC} = \sum_{n=1}^{24} [\text{Volume}(n)] \times [\text{Phase duration}(n)]\right)$.

Aortic flow data (sinotubular junction level) were acquired during a breath-hold using a flow-sensitive gradient-echo sequence (TR = 3.0–6.0 ms; TE = 2.0–3.0 ms; flip angle = 15°; slice thickness = 10 mm; field of view = 360 mm; and matrix = 176 × 256; velocity encoding = 200 cm/s and adjusted appropriately) and aortic flow calculated from phase contrast images.

HH volume increased significantly following feeding (473 ± 546 ml vs. 576 ± 621 ml, P = 0.004; Supplementary figure). LAV_{Max}, LAV_{PreA}, LAV_{Min} and LA multiphasic AUC decreased following feeding (Table 1 and Fig. 1A). The greatest reductions in postprandial LA volumes were observed during the latter half of LA reservoir filling (phases 6–12) and during active LA emptying (phases 20–22) (Fig. 1C). LV end-diastolic volume was unchanged following feeding however LV ejection fraction increased significantly. Despite the increase in LV ejection fraction, net aortic stroke volume did not augment following feeding. The discrepancy between mildly increased LV stroke volume and unchanged aortic stroke volume resulted in a mildly increased mitral regurgitant volume.

☆ Grant support: This study was funded by an investigator-initiated research grant to CN from Pfizer (WS1899830), Australia, a post-graduate research scholarship to CN from the National Health and Medical Research Council (APP1039316) of Australia, and program grant funding to LK from the National Health and Medical Research Council (APP1037903) of Australia. The funding bodies had no role in study design, data collection, analysis or writing of the manuscript.

* Corresponding author.
E-mail address: leonard.kritharides@sydney.edu.au (L. Kritharides).

http://dx.doi.org/10.1016/j.ijcard.2014.12.133
0167-5273/

Table 1
Changes in cardiac parameters following feeding in HH patients.

Cardiac volume	Pre-operative patients N = 10			Post-operative patients N = 5		
	Pre-feeding (N = 10)	Post-feeding (N = 10)	P value*	Pre-feeding N = 5	Post-feeding N = 5	P value*
Left atrial volumes[a]						
Maximal volume	81 ± 17	71 ± 15	0.004	91 ± 18	95 ± 16	0.31
Pre-atrial systole volume	64 ± 12	53 ± 13	0.002	75 ± 22	71 ± 22	0.44
Minimal volume	40 ± 9	35 ± 8	0.03	48 ± 13	48 ± 10	0.81
Left ventricular						
End-diastolic — ml	116 ± 22	118 ± 24	0.43	125 ± 22	127 ± 22	0.63
End-systolic — ml	38 ± 15	33 ± 18	0.09	44 ± 11	38 ± 12	0.13
Stroke volume — ml	78 ± 14	85 ± 12	0.06	81 ± 15	89 ± 14	0.06
Ejection fraction (%)	68 ± 9	74 ± 11	0.01	65 ± 5	71 ± 7	0.06
Right ventricular						
End-diastolic — ml	134 ± 31	132 ± 37	0.82	143 ± 49	143 ± 35	NS
End-systolic — ml	59 ± 23	56 ± 25	0.48	63 ± 27	60 ± 30	0.13
Stroke volume — ml	75 ± 18	76 ± 18	0.48	80 ± 23	83 ± 14	NS
Ejection fraction (%)	57 ± 9	59 ± 11	0.36	57 ± 6	60 ± 12	0.63
Aortic flow and cardiac output						
Forward aortic stroke volume — ml	69 ± 13	70 ± 10	NS	71 ± 17	80 ± 17	0.06
Net aortic stroke volume — ml	67 ± 14	68 ± 11	0.92	68 ± 17	77 ± 16	0.06
Heart rate — bpm	63 ± 10	68 ± 14	0.03	57 ± 13	63 ± 14	0.13
Cardiac output — L/min	4.2 ± 1.2	4.5 ± 0.9	0.06	3.8 ± 0.6	4.7 ± 0.8	0.13
Mitral regurgitant volume and fraction[b]						
Mitral regurgitant volume — ml	9 ± 7	15 ± 9	0.03	10 ± 5	9 ± 6	0.78
Mitral regurgitant fraction — %	11 ± 8	17 ± 10	0.06	13 ± 8	10 ± 7	0.38

NS, not significant.
* P value for Wilcoxon matched pairs test.
[a] Maximal, pre-atrial systole and minimal LA volumes corresponded to phases 11, 21 and 1 in the pre-operative patients and to phases 10, 21 and 1 in the post-operative patients, respectively.
[b] Mitral regurgitant volume = LV stroke volume − aortic forward stroke volume; mitral regurgitant fraction (%) = mitral regurgitant volume × 100% / LV stroke volume.

Post-operatively, HH resolution was achieved in all but 1 patient with a residual hernia. Feeding did not result in any significant change in phasic LA volumes or multiphasic AUC (Fig. 1B). LV stroke volume and net aortic stroke volume increased non-significantly following feeding (Table 1).

The present study is the first to systematically evaluate the acute effects of feeding on cardiac volumes in patients with large HH before and after surgery. The primary observation is that increased hernia volume following feeding acutely reduces LA volumes in patients with large HH and this is abolished by corrective surgery. Prior studies have shown that LA size does not decrease after feeding in normal subjects; indeed feeding was shown to increase the atrial contribution to LV filling [5]. Moreover, physiological states associated with hyperdynamic LV systolic function other than feeding, such as exercise, necessarily rely on increased LA reservoir volume. Thus, decreased postprandial LA volumes in HH patients are likely to be unique to this population and due to the mechanical effects of the hernia rather than the hyperdynamic state of feeding. Importantly, the reduction of LA volumes appeared to be greater during the latter phase of reservoir filling (Fig. 1C). LA filling during this period is primarily determined by passive LA properties including atrial compliance [6], which may be decreased in the setting of extrinsic compression by HH. This is clinically relevant as LA compliance is an independent predictor of exercise impairment in other cardiac conditions [7].

Despite the effect of feeding on LA filling, LV diastolic volume was minimally affected, emphasizing the importance of the LA–LV interaction in preserving LV filling under different LA filling conditions [8]. The observation of hyperdynamic postprandial systolic LV function is consistent with previous studies [9]. Despite hyperdynamic systolic function, aortic stroke volume did not increase following feeding among the pre-operative patients. Inability to augment aortic stroke volume with feeding suggests limited cardiac reserve in HH patients and may contribute to the development of symptoms following exercise in this cohort.

The apparent increase in postprandial mitral regurgitant volume is unexplained. HH can encroach on the mitral annulus and basal posterolateral LV and therefore promote regurgitation by distorting the mitral annulus. The association between mitral valve prolapse and intra-thoracic cardiac entrapment due to reduced antero-posterior diameter supports this hypothesis [10]. However, as the magnitude of increase in postprandial mitral regurgitant volume was small this result should be interpreted cautiously.

The primary limitations of this study are the small sample size and selection bias. Additionally, our studies were only performed at rest and further studies evaluating stroke volume after exercise and feeding are needed to clarify whether these stressors interact unfavorably in the presence of a HH.

In conclusion, increased HH volume following feeding is associated with significantly decreased LA volumes, and this is abolished by corrective surgery. Hyperdynamic LV systolic function following meals results in preserved but not augmented aortic stroke volume suggesting limited cardiac reserve in these patients. These results may contribute to our understanding of the pathophysiology of dyspnea in HH patients.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2014.12.133.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Acknowledgments

The authors would like to thank Helen Lackey for her assistance with conducting the cardiac MRI studies.

References

[1] C. Naoum, et al., Left atrial compression and the mechanism of exercise impairment in patients with a large hiatal hernia, J. Am. Coll. Cardiol. 58 (15) (2011) 1624–1634.
[2] C.W. Siu, et al., Recurrent acute heart failure caused by sliding hiatus hernia, Postgrad. Med. J. 81 (954) (2005) 268–269.

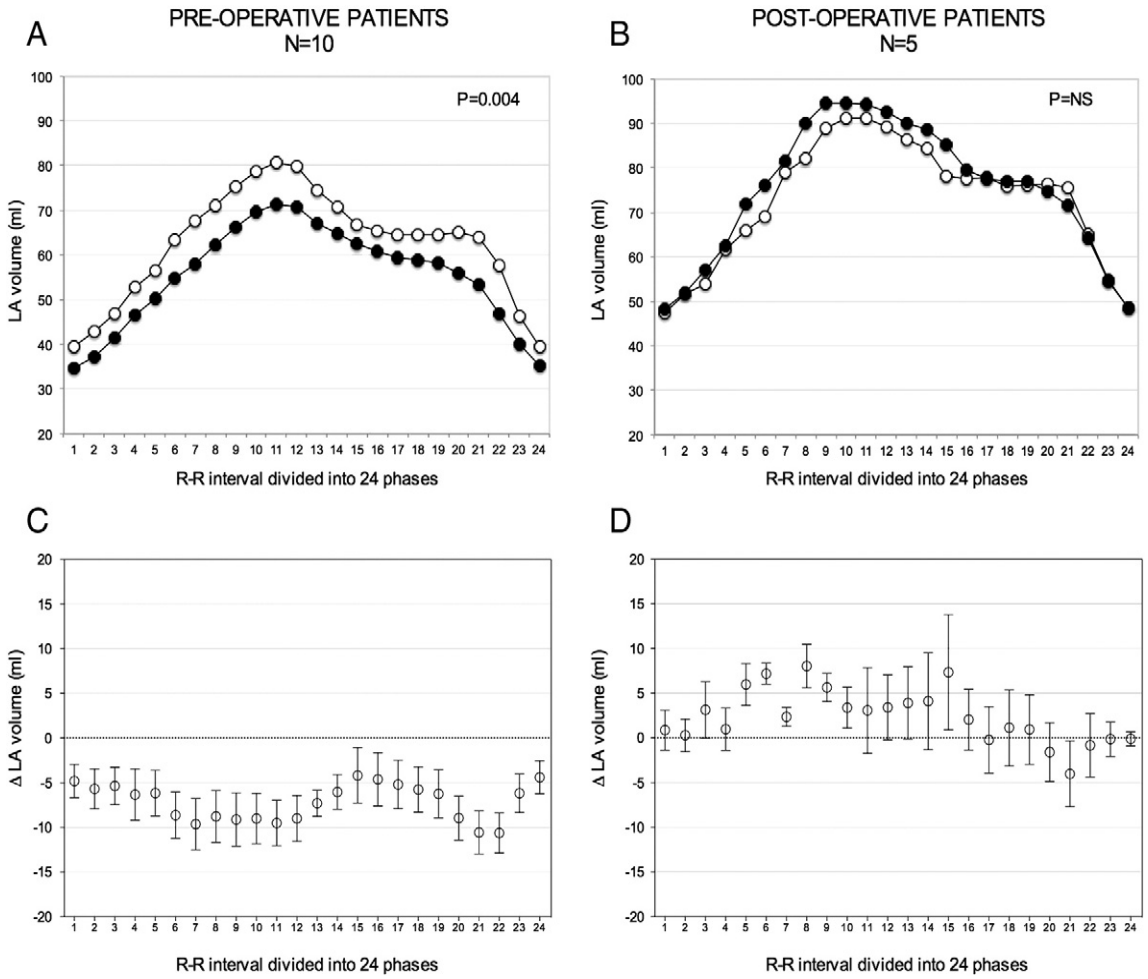


Fig. 1. Mean multiphasic left atrial volumes before **(open symbols)** and after (**closed symbols**) feeding are shown throughout the cardiac cycle in pre-operative (A) and post-operative (B) HH patients. *P value for difference in area under the multiphasic LA volume curve before and after feeding. Mean change (±SEM) in LA volumes are shown in pre-operative (C) and post-operative (D) patients for each phase of the cardiac cycle. SEM, standard error of mean; NS, not significant.

[3] L. Neumann, B. Poulton, S. Ridley, Life-threatening complications of hiatus hernia, Anaesthesia 54 (1) (1999) 93–94.
[4] F. von Knobelsdorff-Brenkenhoff, J. Schulz-Menger, Intrathoracic stomach and the effect of food ingestion on left ventricular stroke volume—a magnetic resonance study, Int. J. Cardiol. 151 (1) (2011) e12–e14.
[5] D.M. Gilligan, et al., Cardiovascular and hormonal responses to a meal in hypertrophic cardiomyopathy: a comparison of patients with and without postprandial exacerbation of symptoms, Clin. Cardiol. 19 (2) (1996) 129–135.
[6] A.F. Leite-Moreira, S.M. Oliveira, P. Marino, Left atrial stiffness and its implications for cardiac function, Future Cardiol. 3 (2) (2007) 175–183.
[7] S. Park, et al., Magnitude of left atrial V wave is the determinant of exercise capacity in patients with mitral stenosis, Am. J. Cardiol. 94 (2) (2004) 243–245.
[8] C. Naoum, et al., Modulation of phasic left atrial function and left ventricular filling in patients with extrinsic left atrial compression by hiatal hernia, Int. J. Cardiol. 176 (3) (2014) 1176–1178.
[9] T.C. Fagan, et al., Postprandial alterations in hemodynamics and blood pressure in normal subjects, Am. J. Cardiol. 58 (7) (1986) 636–641.
[10] P. Raggi, et al., Is mitral valve prolapse due to cardiac entrapment in the chest cavity? A CT view, Chest 117 (3) (2000) 636–642.

Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

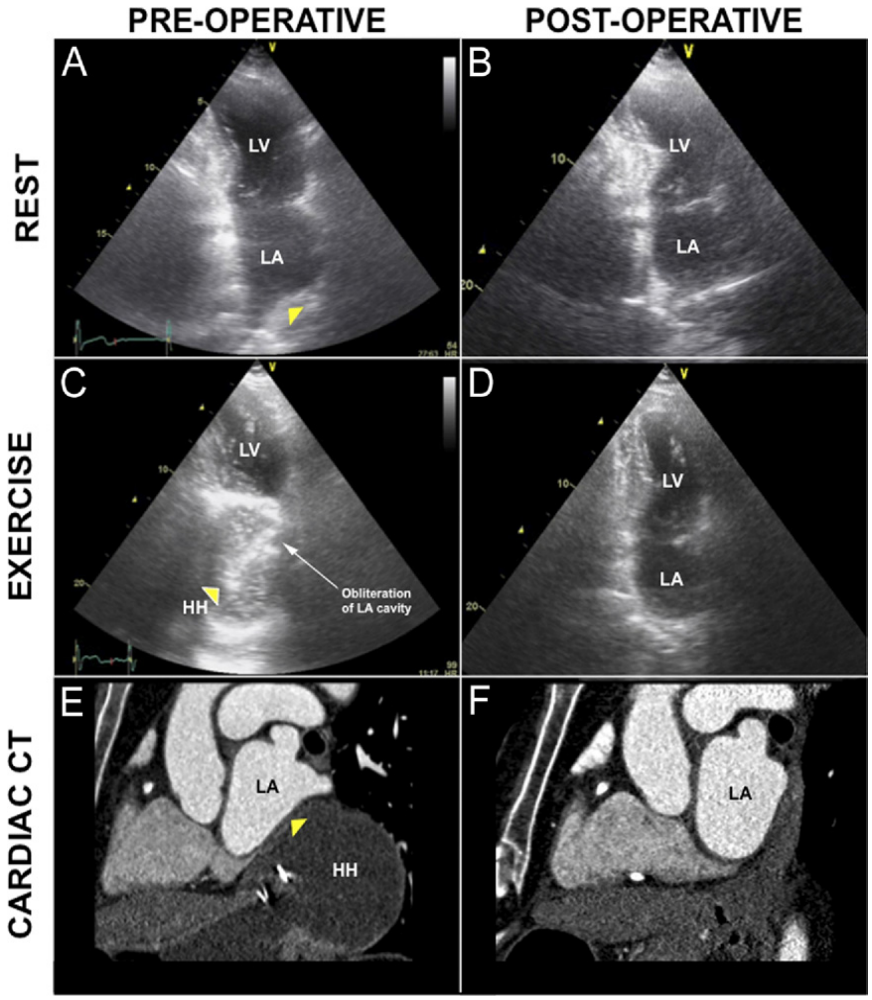
Vol. 58, No. 14, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.03.067

IMAGES IN CARDIOLOGY

Exercise-Induced Left Atrial Compression by a Hiatus Hernia

Christopher Naoum, BSc (Med) MBBS,* Gregory Falk, MBBS,† John Yiannikas, MBBS*

Sydney, Australia



From the *Cardiology Department, Concord Hospital, University of Sydney, Concord, Sydney, Australia; and the †Department of Upper GI Surgery, Concord Hospital, University of Sydney, Concord, Sydney, Australia.
Manuscript received February 23, 2011; accepted March 10, 2011.

A 70-year-old man with a large hiatus hernia (HH) underwent stress echocardiography to investigate exertional dyspnea. His resting echocardiogram showed mild left atrial (LA) compression by an HH **(A)**, confirmed on computed tomography (CT) **(E)**. After 6 min of exercise (Bruce protocol), he experienced severe dyspnea and pre-syncope, and his blood pressure fell from 160/80 to 105/70 mm Hg. Stress echocardiogram revealed almost complete obliteration of the LA cavity by the HH (**C**, Online Video 1). After surgical HH repair, repeat echocardiography and computed tomography showed no evidence of LA compression at rest **(B, F)** or with exercise **(D)**, and his exercise time improved significantly to 11 min.

The close anatomic relationship of HH to the LA allows extrinsic LA compression. With exercise, increased intra-abdominal pressure may force the HH upward, worsen LA compression, and impair left ventricular (LV) filling. Exercise-induced LA compression may be important in explaining exertional dyspnea and pre-syncope in such patients.

Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 58, No. 15, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.07.013

Left Atrial Compression and the Mechanism of Exercise Impairment in Patients With a Large Hiatal Hernia

Christopher Naoum, MBBS,* Gregory L. Falk, MBBS,† Austin C. C. Ng, MBBS, MMED,* Tony Lu, MBBS,‡ Lloyd Ridley, MBBS,‡ Alvin J. Ing, MD,§ Leonard Kritharides, MBBS, PHD,* John Yiannikas, MBBS*

Sydney, New South Wales, Australia

Objectives The purpose of this study was to determine the association between cardiac compression and exercise impairment in patients with a large hiatal hernia (HH).

Background Dyspnea and exercise impairment are common symptoms of a large HH with unknown pathophysiology. Studies evaluating the contribution of cardiac compression to the pathogenesis of these symptoms have not been performed.

Methods We collected clinical data from a consecutive series of 30 patients prospectively evaluated with resting and stress echocardiography, cardiac computed tomography, and respiratory function testing before and after laparoscopic HH repair. Left atrial (LA), inferior pulmonary vein, and coronary sinus compression was analyzed in relation to exercise capacity (metabolic equivalents [METs] achieved on Bruce treadmill protocol).

Results Exertional dyspnea was present in 25 of 30 patients (83%) despite normal mean baseline respiratory function. Moderate to severe LA compression was qualitatively present in 23 of 30 patients (77%) on computed tomography. Right and left inferior pulmonary vein and coronary sinus compression was present in 11 of 30 (37%), 12 of 30 (40%), and 26 of 30 (87%) patients, respectively. Post-operatively, New York Heart Association functional class and exercise capacity improved significantly (number of patients in New York Heart Association functional classes I, II, III, and IV: 6, 11, 11, and 2 vs. 26, 4, 0, and 0, respectively, $p < 0.001$; METs [percentage predicted]: 75 ± 24% vs. 112 ± 23%, $p < 0.001$) and resolution of cardiac compression was observed. Absolute change in LA diameter on the echocardiogram was the only independent cardiorespiratory predictor of exercise capacity improvement post-operatively ($p = 0.006$).

Conclusions We demonstrate, for the first time, marked exercise impairment and cardiac compression in patients with a large HH and normal respiratory function. After HH repair, exercise capacity improves significantly and correlates with resolution of LA compression. (J Am Coll Cardiol 2011;58:1624–34) © 2011 by the American College of Cardiology Foundation

Large hiatal hernias (HHs) are associated with significant morbidity and mortality (1,2). Laparoscopic repair is generally recommended in symptomatic patients due to the risk of life-threatening complications from mechanical obstruction and incarceration (3). Symptoms typically reported include postprandial pain, heartburn, dysphagia, vomiting, and anemia (4). Dyspnea, although common, is an often misdiagnosed or unrecognized symptom in these patients (5). Occasionally, dyspnea is incorrectly attributed to comorbid respiratory or cardiac insufficiency, and patients are denied surgery on the basis of a perceived higher operative risk (6).

See page 1635

Despite the high prevalence of dyspnea in patients with a large HH, its mechanism is unclear. HHs can enlarge with time and cause significant compression and displacement of adjacent intrathoracic structures. Although the effects on respiratory function, diaphragmatic motility, ventilation, and perfusion are intuitively apparent, previous reports quantifying these effects are limited (6–10). Gastroesopha-

From the *Department of Cardiology, Concord Repatriation General Hospital, The University of Sydney, Concord, New South Wales, Australia; †Department of Upper Gastrointestinal Surgery, Concord Repatriation General Hospital, The University of Sydney, Concord, New South Wales, Australia; ‡Department of Radiology, Concord Repatriation General Hospital, The University of Sydney, Concord, New South Wales, Australia; and the §Department of Thoracic Medicine, Concord Repatriation General Hospital, The University of Sydney, Concord, New South Wales, Australia. All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 13, 2011; revised manuscript received June 17, 2011, accepted July 5, 2011.

geal reflux, which is common in HH and associated with respiratory symptoms, appears to have no effect on exercise capacity (11).

The left atrium and pulmonary veins are anatomically adjacent to the enlarging HH (Fig. 1). Case reports and 2 small case series have described cardiac compression by HH, leading to acute heart failure and hemodynamic compromise (12–17). However, there are no systematic studies evaluating the role of cardiac compression in HH-associated dyspnea.

The aim of the present study was to evaluate the functional significance of cardiac compression in relation to dyspnea and exercise capacity and in relation to the recovery of these after laparoscopic HH repair.

Methods

Study design. We prospectively collected clinical data from a consecutive series of patients with a large HH undergoing surgical repair to treat gastrointestinal symptoms (Table 1) (18–22) and prevent mechanical complications. Endoscopic or barium swallow evaluation identified patients with a large HH, defined as a hernia consisting of ≥30% intrathoracic stomach (3). The decision to undertake surgery was made before cardiorespiratory assessment, which included resting and exercise echocardiography, cardiac computed tomography (CT), and respiratory function testing before and after surgery, performed as part of the clinical evaluation. Demographic details, New York Heart Association (NYHA) functional class, symptoms, and comorbidities were collected. Clinical assessment, imaging analyses, and respiratory function testing were independently performed by separate observers. Stress echocardiography was, by clinical necessity, performed without blinding to the resting echocardiographic data. Post-operative imaging was performed knowing that patients had undergone surgery because HHs were immediately apparent (pre-operatively) or absent (post-operatively) on the echocardiogram and CT. Laparoscopic repair involved total sac excision, suture repair of the crural pillars, esophagogastropexy, and 360° fundoplication. Changes in cardiac and respiratory parameters after surgery and their relationship to exercise capacity were evaluated. The institutional Human Research Ethics Committee approved analysis and reporting of data, for which patients provided written informed consent.

Abbreviations and Acronyms

CS = coronary sinus
CT = computed tomography
FEV_1 = forced expiratory volume in the first second of expiration
FVC = forced vital capacity
HH = hiatal hernia
IPV = inferior pulmonary vein
LA = left atrial
MET = metabolic equivalent
NYHA = New York Heart Association

Cardiac CT assessment. Contrast-enhanced cardiac CT was performed using a dual-source, 64-slice helical CT scanner (Somatom Definition, Siemens AG, Erlangen, Germany). One liter of water was orally ingested to distend the HH before image acquisition. The scan was performed during a single breath hold at end-inspiration and after injection of 100 ml of intravenous contrast media (Ultravist 370, Bayer, Leverkusen, Germany). Gating to the cardiac cycle was retrospective with images reconstructed and transferred to a workstation (Syngo 3D, Siemens Medical Solutions, Forchheim, Germany) for offline analysis, using the end-systolic phase.

Compression of the left atrium was qualitatively graded (none, mild, moderate, severe) based on the appearance of the left atrial (LA) contour immediately adjacent to the HH in 2 orthogonal views (Online Fig. 1). A convex appearance in both views was considered normal; flattening in 1 view was considered mild compression; flattening in both views was considered moderate compression; and a concave ap-

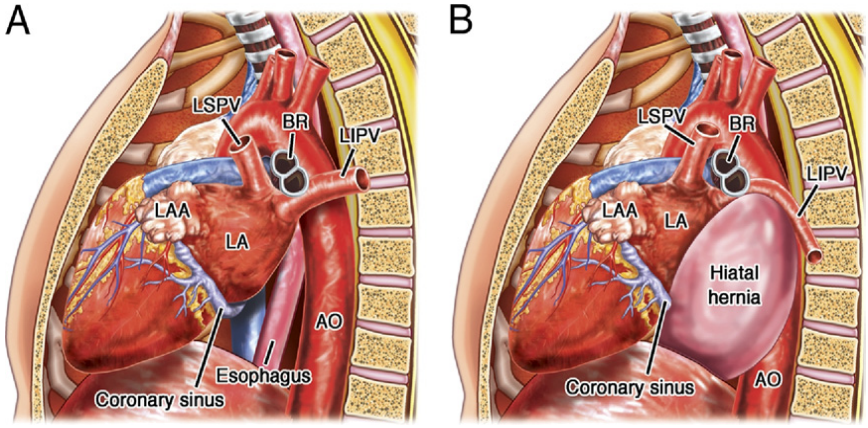


Figure 1 Cardiac and Esophageal Anatomical Relationship

The relevant infero-posterior cardiac structures (coronary sinus, left atrium [LA], and pulmonary veins) and their immediate relationship to the esophagus are demonstrated in the sagittal section **(A)**. Compression by a large hiatal hernia is illustrated in **B** showing progressive involvement, in order, of the coronary sinus, LA, and inferior pulmonary veins with increasing size of the hernia. AO = aorta; BR = bronchus; LAA = left atrial appendage; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein.

Table 1 Baseline Characteristics and Cardiac and Respiratory Function (N = 30)

Demographic and clinical characteristics	
Age, yrs	70 ± 10
Female	23 (77)
Heart rate, beats/min	79 (70–85)
Systolic blood pressure, mm Hg	130 (130–135)
Body mass index, kg/m^2	30.9 (26.6–34.5)
Hiatal hernia size and classification	
Volume on computed tomography, ml	400 (248–596)
Percentage of intrathoracic stomach (intraoperative)	
30%–50%	2 (7)
50%–75%	21 (70)
75%–100%	7 (23)
Classification*	
Type I	0 (0)
Type II	0 (0)
Type III	29 (97)
Type IV	1 (3)
Symptoms	
Cardiorespiratory symptoms	
Dyspnea	
Exertional	25 (83)
Postural	17 (57)
Postprandial	20 (67)
Cough	7 (23)
Chest pain or pressure (noncardiac)	24 (80)
Angina pectoris	1 (3)
Palpitations	7 (23)
Syncope	1 (3)
Orthopnea or paroxysmal nocturnal dyspnea	4 (13)
Ankle swelling	4 (13)
Gastrointestinal symptoms	
Heartburn	18 (60)
Regurgitation	17 (57)
Early satiety	24 (80)
Dysphagia	16 (53)
New York Heart Association functional class	
I	6 (20)
II	11 (37)
III	11 (37)
IV	2 (7)
Patients with comorbidity	
≥1 respiratory conditions on history†	10 (33)
≥1 cardiac conditions on history‡	7 (23)
Cardiac function on Doppler-echocardiography	
Left ventricular function	
LVEF, %	61 ± 9
No. of patients with LVEF <40%	0 (0)
No. of patients with LVEF between 40% and 55%	9 (30)
No. of patients with inducible myocardial ischemia on stress echocardiography	0 (0)
No. of patients with significant valvular heart disease§	2 (7)
Pulmonary hypertension‖	
RVSP, mm Hg	32 ± 8
No. of patients with RVSP >28 mm Hg	10 (33)
Respiratory function testing¶	
Spirometry	
FEV_1, % predicted	99 ± 17
FVC, % predicted	109 ± 19
Forced expiratory ratio (FEV_1/FVC), %#	73 ± 7
Patients with airflow limitation	
Stage I (mild)	7 (23)
Stage II (moderate)	2 (7)
Stage III (severe)	0 (0)
Patients with reversible airflow limitation following bronchodilator	4 (13)
Lung volumes	
Total lung capacity, % predicted	94 ± 14
Residual volume, % predicted	89 ± 17
Patients with abnormal lung volumes	4 (13)
DLCO	
% predicted	74 ± 13
DLCO corrected for alveolar volume, % predicted	75 ± 14
No. of patients with impaired DLCO, % predicted	9 (30)
History of anemia	9 (30)
Hemoglobin, g/l	136 (131–148)
Creatinine clearance, ml/min¶	80 ± 20

Continued in next column

Values are mean ± SD, n (%), or median (interquartile range). *Type I, sliding; type II, paraesophageal; type III, mixed; type IV, mixed plus additional visceral herniation. †Included chronic obstructive pulmonary disease or asthma in 5 of 30 (17%); sleep apnea in 4 of 30 (13%); history of pulmonary embolism in 3 of 30 (10%); bronchitis in 1 of 30 (3%); right upper lobe resection for malignancy in 1 of 30 (3%); and silicosis in 1 of 30 (3%). ‡Included ischemic heart disease in 6 of 30 (20%) and paroxysmal atrial fibrillation in 1 of 30 (3%). §Valvular heart disease was defined as moderate or greater valvular stenosis or regurgitation on qualitative assessment. (Patient #1, moderate aortic and mitral regurgitation; Patient #2: moderate aortic regurgitation). ‖Right ventricular systolic pressure was estimated from the systolic right ventricular to right atrial pressure gradient. Right atrial pressure, assumed to be 5 mm Hg, was then added to the calculated gradient (18). Right ventricular systolic pressure >28 mm Hg was considered elevated (19). TR jets were analyzable in 20 patients (67%). ¶The modification of diet in renal disease formula was used to estimate the creatinine clearance rate. #Normal airflow defined as forced expiratory volume in the first second of expiration (FEV_1)/forced vital capacity (FVC) ratio >70%. In the presence of an FEV_1/FVC ratio <70%, stage I airflow limitation was defined as FEV_1 ≥80%, stage II as FEV_1 between 30% and 80%; stage III as FEV_1 ≤30% (20). Reversible airflow limitation was defined as a >12% (and >200 ml) improvement in either FEV_1 or FVC (21). Normal lung volumes were defined as total lung capacity >80%, and residual volume <120%. Diffusing capacity of lung for carbon monoxide (DLCO) was considered normal if values obtained were >70% of predicted (22).

LVEF = left ventricular ejection fraction; RVSP = right ventricular systolic pressure.

pearance in either view was considered severe compression. LA volume was quantified using 3-dimensional semiautomated software (Syngo Volume, Siemens Medical Solutions). Boundaries of the left atrium were manually traced in multiple axial slices, with exclusion of the pulmonary veins and LA appendage. The software then automatically interpolated regions between the defined regions of interest and calculated volume.

Pulmonary vein compression was qualitatively present if the caliber of the inferior pulmonary vein (IPV) adjacent to the HH appeared significantly reduced compared with the caliber of the superior pulmonary vein on the same side based on previous studies suggesting similar dimensions of the superior pulmonary vein and IPV (23). Minimal and maximal IPV diameters were measured between the ostium

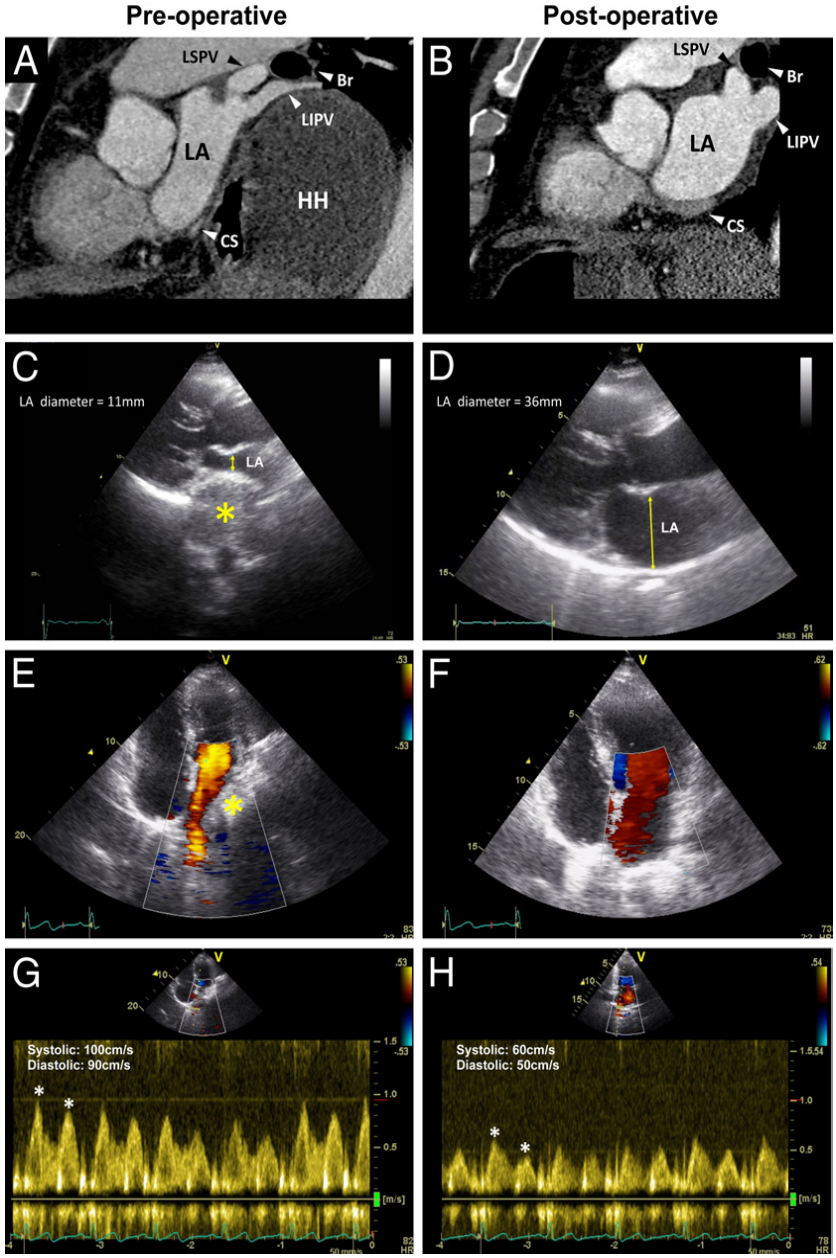


Figure 2 **Cardiac CT and Doppler-Echocardiographic Findings Before and After HH Repair**

(A) Sagittal section summarizing the cardiac computed tomography (CT) abnormalities seen. Left atrial compression by a large hiatal hernia (HH) with flattening of the LA contour is demonstrated. Compression of the LIPV between the HH and a central bronchus, compression of the coronary sinus (CS), and sparing of the left superior pulmonary vein (LSPV) are also seen. **(B)** Post-operatively, there is resolution of cardiac compression with restoration of the size and contour of the LA. **(C)** Parasternal long-axis echocardiographic view demonstrating left atrial compression by a HH **(*)**. Measurement of the left atrial diameter from the midpoints of anterior and posterior left atrial walls is shown. **(D)** Corresponding post-operative view showing resolution of left atrial compression with a significant increase in left atrial diameter. **(E)** Pre-operative apical 4-chamber view with left atrial compression by an HH **(*)** and increased atrial inflow velocity on color Doppler imaging. Peak systolic and diastolic pulse-Doppler velocities at the atrial inflow are shown **(G)**. **(F and H)** Corresponding post-operative view showing a reduction in the atrial inflow velocity on color and pulse-Doppler imaging. Abbreviations as in Figure 1.

and first branch point in 2 orthogonal views to quantify IPV compression, with reporting of the average of these dimensions for each side. Coronary sinus (CS) compression was subjectively assessed (Figs. 2A and 2B) as reported previously (24).

HH volume was quantified using the semiautomated method described previously for LA volume calculation. Left ventricular volumes were calculated (Syngo Circulation, Siemens Medical Solutions) using threshold-based, region-growing, 3-dimensional segmentation of the left ventricle.

Doppler echocardiography assessment. Transthoracic echocardiography was performed (Vivid 7, GE Healthcare, Horten, Norway) with patients instructed to consume a meal 1 h before undergoing echocardiography. Images were stored digitally for offline analysis (Echo Pac

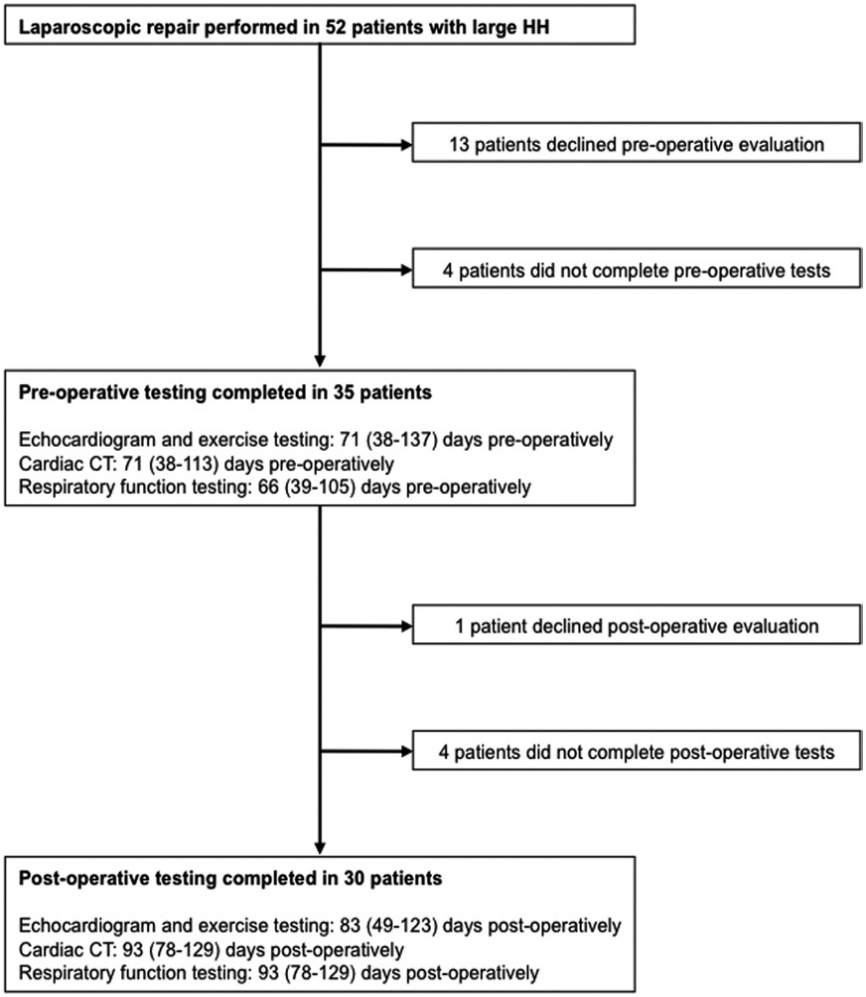


Figure 3 **Patient Evaluation Flowchart**

The final analysis was performed in the 30 patients who completed all pre-operative and post-operative investigations. CT = computed tomography; HH = hiatal hernia.

PC, GE Healthcare). The left ventricular ejection fraction was calculated using Simpson's biplane method (25). The right ventricular systolic pressure was derived from the peak velocity of the tricuspid regurgitant envelope obtained from continuous Doppler imaging (26).

LA compression severity was qualitatively determined (none, mild, moderate, severe) by visual assessment of 4 standard echocardiographic views (Online Fig. 2). This was quantified by measuring the anteroposterior LA diameter at the LA midpoint in the parasternal long-axis view 1 frame before opening of the mitral valve (Figs. 2C and 2D). Peak systolic and diastolic pulse-Doppler velocities at the LA inflow were recorded (Figs. 2E to 2H).

Exercise testing. Exercise testing was performed according to the maximal Bruce treadmill protocol with metabolic equivalents (METs) achieved calculated based on the duration of exercise and exercise capacity defined as the METs achieved expressed as a percentage of age-predicted values (27,28). Stress echocardiographic images were obtained immediately after exercise for offline analysis of regional wall motion to exclude myocardial ischemia. The change in exercise capacity after HH repair was measured as the difference between the post-operative exercise capacity and the pre-operative exercise capacity.

Respiratory function testing. Spirometry, lung volumes (via body plethysmography), and single-breath diffusing capacity of lung for carbon monoxide were measured according to American Thoracic Society criteria using a commercially available system (Vmax Encore, SensorMedics, Yorba Linda, California) (29–31). Respiratory function testing was often performed before the CT scan on the same day, and was always performed without oral loading.

Statistical analysis. Continuous data are expressed as mean ± SD for normally distributed variables and median (interquartile range) otherwise. Parametric and nonparametric analyses (paired and Wilcoxon matched *t* tests, chi-square test for trend) were performed to compare variables before and after surgery, as appropriate. Our primary hypothesis was that LA compression severity correlated with the degree of exercise capacity improvement. We therefore pre-specified LA compression severity into 4 groups (none, mild, moderate, severe).

One-way analysis of variance for linear trend was used to compare means among multiple groups. A 2-tailed $p < 0.05$ was considered significant.

The improvement in exercise capacity after HH repair was evaluated in relation to the improvement in cardiac and respiratory variables after HH repair, using linear regression analysis. Multiple linear regression analysis, including parameters that improved significantly post-operatively and had a univariate $p < 0.05$, was performed to identify changes in cardiorespiratory variables that independently predicted exercise capacity improvement. Within each category (cardiac and respiratory), less significant univariables correlating significantly ($R > 0.6$) with other univariables in the model were removed to avoid multicollinearity. Statistical analysis was performed using Prism 5.0b and Instat 3.1a (GraphPad Software, La Jolla, California).

Results

Between 2009 and 2010, 52 consecutive patients with large and symptomatic HHs underwent laparoscopic repair, of whom 30 underwent all pre-operative and post-operative investigations and were included in the final analysis (Fig. 3).

Baseline characteristics are summarized in Table 1. Exertional dyspnea was reported by the majority of patients (25 of 30, 83%) despite minimal rates of significant cardiac or respiratory disease. The mean left ventricular ejection fraction was normal (61 ± 9%), and there were no patients with a left ventricular ejection fraction <40% or inducible myocardial ischemia. Two patients had moderate valvular heart disease. Mean spirometric, lung volume, and diffusing capacity of lung for carbon monoxide values, as percentages of predicted, were normal at baseline. A history of anemia was reported in 9 of 30 patients (30%); however, the measured hemoglobin at pre-operative assessment was normal for the overall cohort (136 g/l [interquartile range: 131 to 148 g/l).

Surgery. Laparoscopic repair was achieved in all but 2 patients who required conversion to open laparotomy. Complications occurred in 3 patients. A wound infection and post-operative respiratory failure requiring invasive ventilation developed in 1 patient. One sustained inadvertent colonic injury during dissection of adhesions. The third patient had a perioperative myocardial infarction, despite normal findings on the pre-operative stress echocardiogram. Coronary angiography was subsequently performed, which demonstrated minor coronary artery disease. There were no deaths in-hospital or at 30 days.

Cardiac CT and Doppler echocardiography findings. CS compression was the most frequently detected abnormality (26 of 30, 87%). Moderate to severe LA compression was observed in the majority of patients by qualitative assessment on cardiac CT (none: 4 of 30, 13%; mild: 3 of 30, 10%; moderate: 14 of 30, 47%; severe: 9 of 30, 30%) and echocardiogram (none: 2 of 30, 7%; mild: 8 of 30, 27%; moderate: 13 of 30, 43%; severe: 7 of 30, 23%). The right

Quantitative Cardiac Parameters Before and After Hiatal Hernia Repair Stratified by Left Atrial Compression Severity

	All Patients (n = 30)			No LA Compression (n = 2)			Mild LA Compression (n = 8)			Moderate LA Compression (n = 13)			Severe LA Compression (n = 7)		
Echocardiography	Pre-Operation	Post-Operation	p Value	Pre-Operation	Post-Operation	p Value	Pre-Operation	Post-Operation	p Value	Pre-Operation	Post-Operation	p Value	Pre-Operation	Post-Operation	p Value
LA diameter, mm	25 ± 8	36 ± 6	<0.001	31 ± 7	30 ± 8	†	33 ± 7	37 ± 7	0.13	24 ± 6	36 ± 6	<0.001	17 ± 5	36 ± 5	<0.001
LA inflow velocity, cm/s*															
Systolic	88 ± 24	74 ± 16	0.003	77 ± 8	85 ± 6	†	79 ± 15	75 ± 17	0.68	87 ± 25	72 ± 15	0.04	103 ± 29	73 ± 19	0.002
Diastolic	72 ± 23	54 ± 16	0.004	59 ± 18	60 ± 6	†	69 ± 22	57 ± 18	0.24	70 ± 23	55 ± 19	0.09	86 ± 27	47 ± 8	0.04

	All Patients (n = 30)			No LA Compression (n = 4)			Mild LA Compression (n = 3)			Moderate LA Compression (n = 14)			Severe LA Compression (n = 9)		
Cardiac CT	Pre-Operation	Post-Operation	p Value	Pre-Operation	Post-Operation	p Value	Pre-Operation	Post-Operation	p Value	Pre-Operation	Post-Operation	p Value	Pre-Operation	Post-Operation	p Value
LA volume, ml	86 (74–97)	95 (80–108)	0.003	98 (76–127)	89 (72–111)	0.43	102 (96–130)	111 (111–130)	0.21	87 (74–95)	91 (80–102)	0.01	77 (68–82)	95 (82–103)	0.002
IPV diameter															
Right, mm	14 (13–15)	15 (14–16)	0.01	14 (13–19)	14 (13–17)	0.38	16 (15–21)	16 (14–16)	0.59	13 (12–14)	15 (14–16)	0.004	14 (10–16)	15 (15–16)	0.04
Left, mm	13 (11–15)	15 (13–17)	<0.001	13 (11–15)	12 (11–14)	0.10	13 (11–16)	19 (15–20)	0.13	14 (11–15)	15 (13–17)	0.003	12 (11–14)	15 (13–16)	0.02
LV volumes, ml															
End-diastolic	119 (90–136)	126 (94–151)	0.15	112 (88–180)	124 (84–166)	0.87	140 (117–176)	133 (73–174)	0.31	120 (99–140)	126 (109–148)	0.38	88 (66–126)	116 (82–151)	0.01
End-systolic	37 (25–52)	44 (30–58)	0.11	37 (27–55)	38 (27–56)	NS	46 (28–64)	58 (34–58)	0.59	35 (27–56)	37 (28–59)	0.78	33 (23–52)	52 (32–61)	0.02

Values are mean ± SD or median (interquartile range). *Diastolic atrial inflow velocity could not be obtained in 5 patients (1 with mild, 2 with moderate, and 2 with severe LA compression). †Insufficient sample size to perform paired t-test.
CT = computed tomography; IPV = inferior pulmonary vein; LA = left atrium; LV = left ventricle; NS = not significant.

Table 3 Respiratory Function Before and After Hiatal Hernia Repair

	Pre-Operative (n = 30)	Post-Operative (n = 30)	p Value
Spirometry			
FEV_1, l	2.11 (1.37–2.45)	2.18 (1.69–2.50)	0.03
% of predicted value	99 (85–108)	103 (98–117)	0.01
	99 ± 17	107 ± 19	
FVC, l	2.72 (2.03–3.48)	2.98 (2.46–3.63)	0.001
% of predicted value	105 (94–122)	118 (108–135)	<0.001
	109 ± 19	121 ± 19	
Ratio of FEV_1 to FVC	72 (69–78)	71 (68–75)	0.05
	73 ± 7	71 ± 6	
Lung volumes			
Total lung capacity, l	4.52 (3.75–5.67)	4.62 (4.06–5.53)	0.03
% of predicted value	92 (86–99)	96 (89–105)	0.006
	94 ± 14	98 ± 10	
Residual volume, l	1.85 (1.48–2.15)	1.69 (1.53–1.92)	0.10
% of predicted value	88 (81–100)	83 (73–97)	0.11
	89 ± 17	84 ± 14	
Diffusing capacity of lung for carbon monoxide, ml/mm Hg/min	15.15 (12.73–17.25)	15.20 (12.55–18.08)	0.32
% of predicted value	76 (67–83)	79 (66–85)	0.27
	74 ± 13	76 ± 13	
Adjusted for alveolar volume, ml/mm Hg/min/l	4.29 (3.58–4.79)	4.09 (3.65–4.51)	0.96
% of predicted value	78 (66–84)	72 (63–77)	0.008
	75 ± 14	71 ± 12	

Values are median (interquartile range) or mean ± SD.
FEV_1 = forced expiratory volume in 1 s; FVC = forced vital capacity.

and left IPVs were compressed in 11 of 30 patients (37%) and 12 of 30 patients (40%), respectively. There were high levels of interobserver agreement for qualitative assessments (Online Figs. 1 and 2).

Quantitative cardiac parameters are presented in Table 2. On cardiac CT, LA volume and left and right IPV diameters improved significantly after surgery. In patients with severe LA compression at baseline, there was a significant increase in left ventricular end-diastolic and end-systolic volumes after surgery, consistent with improved ventricular filling. On the echocardiogram, the LA diameter increased significantly after HH repair (25 ± 8 mm vs. 36 ± 6 mm, $p < 0.001$). The pre-operative atrial inflow peak systolic and diastolic velocities were 88 ± 24 cm/s and 72 ± 23 cm/s, respectively. These decreased significantly after surgery to 74 ± 16 cm/s ($p = 0.003$) and 54 ± 16 cm/s ($p = 0.004$), respectively. The absolute reduction in systolic atrial inflow velocity after surgery was greater in patients with moderate to severe versus none to mild LA compression (21 ± 23 cm/s vs. 1 ± 22 cm/s, $p = 0.03$).

Respiratory function. Airflow limitation was present in 9 of 30 patients (30%); however, this was only mild in 7 of 30

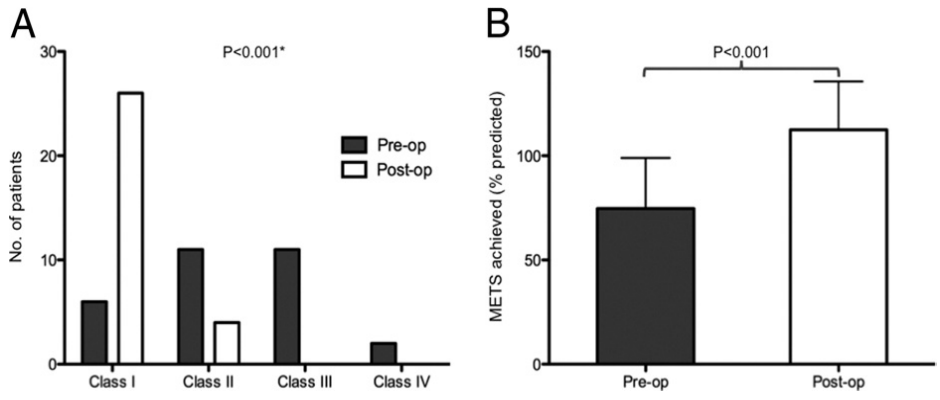


Figure 4 Change in Functional Class and Exercise Capacity After HH Repair

Change in New York Heart Association functional class **(A)** and mean exercise capacity **(B)** after hiatal hernia repair. Exercise capacity defined as metabolic equivalents (METS) achieved expressed as a percentage of age-predicted values. *p value for chi-square test for trend.

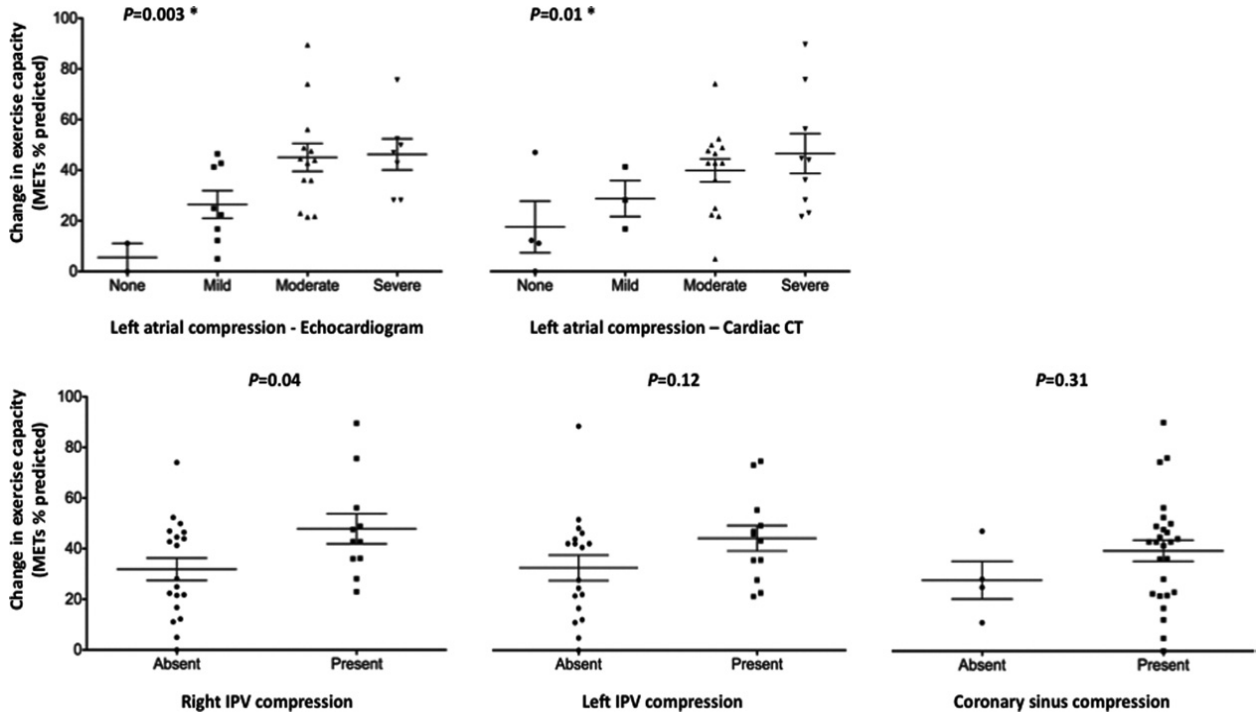


Figure 5 **Relationship Between Baseline Cardiac Compression and Change in Exercise Capacity After HH Repair**

Pre-operatively, qualitative assessment of left atrial (LA) compression on echocardiography and LA and right inferior pulmonary vein (IPV) compression on cardiac computed tomography (CT) predict a greater increase in exercise capacity after hiatal hernia (HH) repair. Change in exercise capacity is defined as post-operative exercise capacity minus pre-operative exercise capacity. *p value for linear trend. MET = metabolic equivalent.

patients (23%) and moderate in 2 of 30 patients (7%). Abnormal lung volumes were present in 4 of 30 patients (13%) (Table 1). Post-operatively, there was a modest but statistically significant increase in forced expiratory volume in the first second of expiration (FEV_1), forced vital capacity (FVC), and total lung capacity (Table 3).

Exercise capacity and functional class. Exercise capacity was reduced at baseline to 75 ± 24% of predicted (6.2 ± 2.4 METs), increasing to 112 ± 23% of predicted (9.2 ± 2.4 METs) after HH repair ($p < 0.001$). NYHA functional class was similarly impaired pre-operatively and improved after surgery (Fig. 4).

The change in exercise capacity after surgery was greater in patients with a higher grade of qualitative LA compression at baseline on either echocardiography or cardiac CT and in patients with right IPV compression. A similar trend was observed in patients with compression of the left IPV; however, this was not statistically significant. CS compression did not predict a greater change in exercise capacity (Fig. 5).

Linear regression analysis demonstrated a significant correlation between the improvement in exercise capacity after surgery and changes to the LA diameter on echocardiography; right IPV diameter on CT; and FEV_1 (percentage predicted), FVC (percentage predicted) and diffusing capacity of lung for carbon monoxide (percentage predicted) on respiratory function tests. Multivariable linear regression analysis identified the only independent predictor to be change in the LA diameter on echocardiogram ($p = 0.006$) (Table 4).

Discussion

The present study identifies for the first time that significant exercise impairment and extrinsic cardiac compression are common in patients with a large HH despite normal mean baseline respiratory function. The recovery of exercise capacity and cardiac parameters after laparoscopic repair indicate that large HHs directly impair exercise capacity that is due, in part at least, to cardiac compression.

A major finding of the present study is that dyspnea is common among patients with a large HH presenting for surgical repair, with 83% of patients reporting this symptom in our group. Although Low and Simchuk (6) reported a similar prevalence of 84% in their cohort, most large studies of HHs do not describe dyspnea and exercise impairment as prominent symptoms (4,5). This is important because laparoscopic surgery is generally reserved for symptomatic patients (3). Importantly, our patients had minimal evidence of severe cardiac or respiratory disease at baseline, indicating that exercise tolerance and dyspnea cannot be simply attributed to comorbidities. Moreover, patients represented their own controls, such that any observed change in exercise capacity after surgery can be confidently attributed to surgical correction of the HH.

Table 4 Relationship Between Exercise Capacity Improvement Following Hiatal Hernia Repair and Changes in Cardiorespiratory Parameters

Cardiorespiratory Parameter	Mean Change Post-Operation	Univariate Analysis*		Multivariate Analysis†	
		R^2	p Value	Regression Coefficient	p Value
Echocardiographic					
LA diameter, mm	11 ± 9	0.34	<0.001	10.3 (3.4)	0.006
LA inflow velocities, cm/s					
Systolic	−14 ± 24	0.12	0.06	—	—
Diastolic	−17 ± 26	0.03	0.45	—	—
RVSP, mm Hg	2 ± 13	0.01	0.71	—	—
LV ejection fraction	−1 ± 11	0.0004	0.92	—	—
Cardiac CT					
LA volume, ml	9 ± 15	0.02	0.47	—	—
IPV diameter, mm				—	—
Right	1 ± 2	0.18	0.02	18.9 (11.0)	0.10
Left	2 ± 2	0.08	0.15	—	—
LV volumes, ml					
End-diastolic	7 ± 23	0.0005	0.91	—	—
End-systolic	3 ± 13	0.01	0.64	—	—
Respiratory function					
FEV_1 (% predicted)	9 ± 17	0.16	0.03	‡	‡
FVC (% predicted)	13 ± 19	0.31	0.001	0.20 (0.16)	0.24
FEV_1/FVC ratio	−2 ± 6	0.07	0.16	—	—
TLC (% predicted)	4 ± 11	0.07	0.16	—	—
RV (% predicted)	−5 ± 15	0.09	0.13	—	—
DLCO (% predicted)	2 ± 9	0.14	0.048	—	—
DLCO/Va (% predicted)	−5 ± 9	0.01	0.54	—	—

Values are mean ± SD. Exercise capacity defined as METs achieved expressed as percentage of predicted. Change in exercise capacity = post-operative exercise capacity – pre-operative exercise capacity. Change in cardio-respiratory parameters = post-operative value – pre-operative value. *Univariate analysis with coefficient of determination (R^2) and p value for simple linear regression assessing relationship between change in cardio-respiratory parameters and change in exercise capacity. †Multivariate analysis performed excluding cardio-respiratory parameters with univariate $p > 0.05$ (—). Regression coefficient and p value testing the contribution of individual variables to the overall multivariate model are reported. Regression coefficients expressed as value (SE). Combined $R^2 = 0.54$, $p < 0.001$ for overall model. ‡FEV_1 (% predicted) excluded from the multivariate model to avoid multicollinearity as it correlated significantly with FVC (% predicted), correlation coefficient, $R = 0.89$.

DLCO = diffusion capacity for carbon monoxide; DLCO/Va = diffusion capacity for carbon monoxide corrected for alveolar volume; RV = residual volume; RVSP = right ventricular systolic pressure; TLC = total lung capacity.

Previous studies suggest that dyspnea in HHs is predominantly due to a mechanical respiratory effect of a large space-occupying intrathoracic mass. In the study by Low and Simchuk (6), only mild abnormalities of spirometry were identified (FEV_1 [percentage predicted] and FVC [percentage predicted], 76% and 79%, respectively), despite moderately severe symptoms. After surgery, dyspneic symptoms completely resolved in most of their patients; however, there was only a mild improvement in spirometric values (absolute increase in both FEV_1 [percentage predicted] and FVC [percentage predicted] of 13%) (6). In the present study, we demonstrated normal mean spirometry at baseline, despite significant dyspnea and exercise impairment. Studies correlating respiratory symptoms with spirometry suggest that the likelihood of reporting dyspnea only increases significantly in the general population when FEV_1 (percentage of predicted) decreases to <75%, which is significantly lower than the mean baseline value in our study (32). After surgery, there was a significant improvement in spirometry (9% and 13% absolute increase in FEV_1 [% predicted] and FVC [% predicted], respectively); however, such degrees of improvement, when observed in patients receiving bronchodilator therapy for chronic obstructive pulmonary disease, do not result in the magnitude of exercise capacity improvement observed in our cohort (33).

Unlike the relatively mild impairment of basal respiratory function in some of our patients, most demonstrated moderate to severe LA compression on echocardiography and cardiac CT, both qualitatively and quantitatively. Many patients also demonstrated compression of the IPVs and increased pulse-Doppler velocity at the LA inflow, implying that extrinsic compression was functionally important. After surgery, resolution of these cardiac abnormalities was accompanied by significant improvement in dyspnea and exercise capacity. The degree of improvement in exercise capacity with surgery correlated with the qualitative assessment of preoperative LA compression severity (Fig. 5).

The relationship among the recovery of exercise capacity, the resolution of cardiac compression, and improvement in respiratory function were explored in this study. Multivariable regression analysis demonstrated that the only independent predictor of improved exercise capacity after HH repair was the change in the LA diameter on echocardiog-

raphy (Table 4). Changes in respiratory variables after HH repair did not independently predict exercise capacity improvement. These data, coupled with the normal mean baseline respiratory function, suggest that although respiratory dysfunction contributes to HH-associated dyspnea, extrinsic cardiac compression may play a more important role in the pathogenesis.

LA compression may cause dyspnea by increasing the pulmonary venous pressure, producing interstitial edema and reduced pulmonary compliance. Previous case reports describing cardiac failure and dyspnea attributable to LA compression by HH support this hypothesis (16,34). Echocardiographic demonstration of pulmonary vein compression by various pathologies has been described in previous case reports, but not in patients with large HHs (35,36). These reports demonstrated increased systolic and diastolic components of the pulse-wave Doppler signal at the pulmonary vein ostium. Our findings of increased velocities at the LA inflow, which resolve significantly after surgery, may represent a similar pathophysiologic process related to compression by the HH.

Extrinsic cardiac compression also appears to have an effect on left ventricular filling because patients with severe LA compression had improved ventricular volumes after HH repair. Case reports of HH causing hemodynamic instability including hypotension requiring inotropic therapy or resulting in syncope are consistent with these findings (14,37–39). Impaired ventricular filling due to LA compression may also contribute to exercise intolerance by preventing the necessary increase in cardiac output that normally occurs with exercise.

Compression of the CS was present in 87% of patients. The anatomic course of the CS in the posterior atrioventricular groove makes it particularly susceptible to compression. However, CS compression was not a useful predictor of improved exercise capacity after surgery. This may be due to the observation that with a binary qualitative method for determining CS compression, most patients demonstrate this abnormality, making it a nondiscriminatory variable in this population. CS compression leading to diastolic dysfunction and dyspnea has been described in a patient with lymphoma, but not in patients with a HH (40). Previous animal studies have confirmed a relationship among CS compression and impaired myocardial blood flow, increased ventricular blood volume, decreased ventricular distensibility, and diastolic dysfunction (41–43). These may represent further mechanisms of impaired exercise capacity due to cardiac compression by HH.

Study limitations. Although the present study is the first to evaluate the relationship between cardiac compression and exercise impairment in patients with a large HH, there are several limitations. First, the cohort only included patients with large and symptomatic HHs in whom surgery was already considered appropriate management. Second, we cannot exclude the possibility of a placebo effect of surgery in relation to symptoms and exercise capacity; however, this is unlikely to explain the magnitude of observed improvement in exercise capacity. Studies evaluating intensive exercise training have demonstrated a significantly smaller degree of improved exercise capacity than that seen after HH repair in our patients (44). Third, the absence of an oral load before respiratory investigation may have led to underestimation of the respiratory effect of HH; however, this was consistent for pre-operative and post-operative evaluations. Finally, some of the measures of cardiac compression were subjective; however, there was a good level of interobserver agreement in the evaluation of these parameters, and almost all qualitative evaluations were independently corroborated by quantification.

Conclusions

Patients with large HHs have significant dyspnea and exercise impairment despite normal baseline respiratory function. We show, for the first time, that significant cardiac abnormalities including compression of the left atrium, IPVs, and CS are commonly seen in these patients. The recovery of exercise capacity with HH repair is independently predicted by recovery of the LA diameter, suggesting a significant causal role for cardiac compression in the pathogenesis of HH-associated dyspnea. Assessment of LA compression severity pre-operatively may be a useful noninvasive clinical tool for identifying those patients who will benefit most from HH repair.

Acknowledgment

The authors thank Prof. Jennifer Peat for her contributions in reviewing the statistical analyses.

Reprint requests and correspondence: Dr. John Yiannikas, Department of Cardiology, Concord Repatriation General Hospital, Hospital Road, Concord, New South Wales, 2139, Australia. E-mail: john.yiannikas@yahoo.com.au.

REFERENCES

1. Skinner DB, Belsey RH. Surgical management of esophageal reflux and hiatus hernia. Long-term results with 1,030 patients. J Thorac Cardiovasc Surg 1967;53:33–54.
2. Sihvo EI, Salo JA, Rasanen JV, Rantanen TK. Fatal complications of adult paraesophageal hernia: a population-based study. J Thorac Cardiovasc Surg 2009;137:419–24.
3. Mitiek MO, Andrade RS. Giant hiatal hernia. Ann Thorac Surg 2010;89:S2168–73.
4. Pierre AF, Luketich JD, Fernando HC, et al. Results of laparoscopic repair of giant paraesophageal hernias: 200 consecutive patients. Ann Thorac Surg 2002;74:1909–15.
5. Maziak DE, Todd TR, Pearson FG. Massive hiatus hernia: evaluation and surgical management. J Thorac Cardiovasc Surg 1998;115:53–60.
6. Low DE, Simchuk EJ. Effect of paraesophageal hernia repair on pulmonary function. Ann Thorac Surg 2002;74:333–7.
7. Selmonosky CA, Blanc JS, Byrd R. Hiatal hernia and pulmonary function impairment: incidence or coincidence? South Med J 1980; 73:1234–6.
8. Senyk J, Arborelius M Jr., Lilja B, Ohlsson NM. Respiratory function in esophageal hiatus hernia. I. Spirometry, gas distribution, and arterial blood gases. Respiration 1975;32:93–102.

9. Senyk J, Arborelius M Jr., Lilja B. Respiratory function in esophageal hiatus hernia. II. Regional lung function. Respiration 1975;32:103–11.
10. Zhu JC, Becerril G, Marasovic K, Ing AJ, Falk GL. Laparoscopic repair of large hiatal hernia: impact on dyspnoea. Surg Endosc 2011 Jun 3 [Epub ahead of print].
11. Giannikoulis C, Karkoulias K, Thomopoulos K, et al. Patients with gastroesophageal reflux disease and respiratory manifestations do not present lung function disorders during cardiopulmonary exercise test. Dis Esophagus 2011;24:189–93.
12. D'Cruz IA, Hancock HL. Echocardiographic characteristics of diaphragmatic hiatus hernia. Am J Cardiol 1995;75:308–10.
13. Nishimura RA, Tajik AJ, Schattenberg TT, Seward JB. Diaphragmatic hernia mimicking an atrial mass: a two-dimensional echocardiographic pitfall. J Am Coll Cardiol 1985;5:992–5.
14. Devbhandari MP, Khan MA, Hooper TL. Cardiac compression following cardiac surgery due to unrecognised hiatus hernia. Eur J Cardiothorac Surg 2007;32:813–5.
15. Hunt GS, Gilchrist DM, Hirji MK. Cardiac compression and decompensation due to hiatus hernia. Can J Cardiol 1996;12:295–6.
16. Siu CW, Jim MH, Ho HH, et al. Recurrent acute heart failure caused by sliding hiatus hernia. Postgrad Med J 2005;81:268–9.
17. Chan J, Manning WJ, Appelbaum E, Smith P, Rice K. Large hiatal hernia mimicking left atrial mass: a multimodality diagnosis. J Am Coll Cardiol 2009;54:569.
18. Lam CS, Borlaug BA, Kane GC, et al. Age-associated increases in pulmonary artery systolic pressure in the general population. Circulation 2009;119:2663–70.
19. Anderson B. Echocardiography. The Normal Examination and Echocardiographic Measurements. 2nd edition. Brisbane, Australia: MGA Graphics, 2004.
20. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med 2001;163:1256–76.
21. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948–68.
22. Aduen JF, Zisman DA, Mobin SI, et al. Retrospective study of pulmonary function tests in patients presenting with isolated reduction in single-breath diffusion capacity: implications for the diagnosis of combined obstructive and restrictive lung disease. Mayo Clin Proc 2007;82:48–54.
23. Schwartzman D, Lacomis J, Wigginton WG. Characterization of left atrium and distal pulmonary vein morphology using multidimensional computed tomography. J Am Coll Cardiol 2003;41:1349–57.
24. Gold MM, Spindola-Franco H, Jain VR, Spevack DM, Haramati LB. Coronary sinus compression: an early computed tomographic sign of cardiac tamponade. J Comput Assist Tomogr 2008;32:72–7.
25. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.
26. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation 1984;70:657–62.
27. Bruce RA. Exercise testing of patients with coronary heart disease. Principles and normal standards for evaluation. Ann Clin Res 1971;3:323–32.
28. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. Am Heart J 1973;85:546–62.
29. Miller MR, Hankinson J, Brusasco V, et al. ATS/ERS Task Force: Standardisation of spirometry. Eur Respir J 2005;26:319–38.
30. Wanger J, Clausen JL, Coates A, et al. ATS/ERS Task Force: standardisation of the measurement of lung volumes. Eur Respir J 2005;26:511–22.
31. Macintyre N, Crapo RO, Viegi G, et al. ATS/ERS Task Force: Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005;26:720–35.
32. Jakeways N, McKeever T, Lewis SA, Weiss ST, Britton J. Relationship between FEV1 reduction and respiratory symptoms in the general population. Eur Respir J 2003;21:658–63.
33. Liesker JJ, Wijkstra PJ, Ten Hacken NH, et al. A systematic review of the effects of bronchodilators on exercise capacity in patients with COPD. Chest 2002;121:597–608.
34. Raza ST, Mukherjee SK, Danias PG, et al. Hemodynamically significant extrinsic left atrial compression by gastric structures in the mediastinum. Ann Intern Med 1995;123:114–6.
35. Chen CL, Tunick PA, Kronzon I. Pulmonary vein compression by tumor: an unusual Doppler flow pattern. Echocardiography 2005;22:746–7.
36. Ikonomidis I, Nikolaou M, Paraskevaidis I, Lekakis J, Kremastinos DT. A case of pulmonary vein obstruction: evaluation using newer echocardiographic imaging techniques. Eur J Echocardiogr 2008;9:133–5.
37. Neumann L, Poulton B, Ridley S. Life-threatening complications of hiatus hernia. Anaesthesia 1999;54:93–4.
38. Oishi Y, Ishimoto T, Nagase N, et al. Syncope upon swallowing caused by an esophageal hiatal hernia compressing the left atrium: a case report. Echocardiography 2004;21:61–4.
39. Maekawa T, Suematsu M, Shimada T, Go M. Unusual swallow syncope caused by huge hiatal hernia. Intern Med 2002;41:199–201.
40. Park SM, Shim CY, Choi D, et al. Coronary sinus obstruction by primary cardiac lymphoma as a cause of dyspnea due to significant diastolic dysfunction and elevated filling pressures. J Am Soc Echocardiogr 2010;23:682.
41. Miura T, Hiramatsu T, Forbess JM, Mayer JE Jr. Effects of elevated coronary sinus pressure on coronary blood flow and left ventricular function. Implications after the Fontan operation. Circulation 1995;92:II298–303.
42. Gaasch WH, Bing OH, Franklin A, et al. The influence of acute alterations in coronary blood flow on left ventricular diastolic compliance and wall thickness. Eur J Cardiol 1978;7 Suppl:147–61.
43. Vogel WM, Apstein CS, Briggs LL, Gaasch WH, Ahn J. Acute alterations in left ventricular diastolic chamber stiffness. Role of the "erectile" effect of coronary arterial pressure and flow in normal and damaged hearts. Circ Res 1982;51:465–78.
44. Kitzman DW, Brubaker PH, Morgan TM, Stewart KP, Little WC. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. Circ Heart Fail 2010;3:659–67.

Key Words: exercise capacity ■ hiatal hernia ■ left atrial compression.

APPENDIX

For supplemental figures, please see the online version of this article.

Surg Endosc (2011) 25:3620–3626
DOI 10.1007/s00464-011-1768-0

Laparoscopic repair of large hiatal hernia: impact on dyspnoea

Jacqui C. Zhu · Guillermo Becerril · Katy Marasovic · Alvin J. Ing · Gregory L. Falk

Received: 15 September 2010 / Accepted: 5 May 2011 / Published online: 3 June 2011

Abstract
Introduction This study aims to examine the impact of laparoscopic repair of large hiatal hernia on dyspnoea severity, respiratory function and quality of life.
Methods From 2004 to 2008, 30 consecutive patients with large para-oesophageal hernia defined as >50% of stomach in the intra-thoracic cavity and minimum follow-up of 2 years were included in this study. All patients had a formal respiratory function test 1 week prior and 3 months after their laparoscopic hiatal hernia repair. Patients rated symptom severity and completed a quality-of-life questionnaire [Gastrointestinal Quality of Life Index (GIQLI)] pre-operatively, and post-operatively at 3 months, 6 months and yearly thereafter.
Results There was no hospital mortality, and the morbidity rate was 10%. In 26 patients with pre-operative dyspnoea, 22 had complete resolution while the remaining 4 had improvement of dyspnoea severity post-operatively. The mean dyspnoea severity index reduced from 2.4 to 1.3 ($P < 0.001$). Overall, there was 1%, 3% and 3% post-operative increase in forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) values for the whole group, none of which reached statistical significance. For patients with resolution or improvement of dyspnoea after laparoscopic repair, no significant change of respiratory function parameters was demonstrated. GIQLI score improved from a pre-operative value of 85.7 to 107.9 post-operatively ($P < 0.001$).
Conclusions We failed to show a significant change in post-operative respiratory function despite clearly demonstrated improvement of respiratory symptoms. Alternative explanations for reduction of dyspnoea severity should be sought.

Keywords Hernia · GORD/GERD (Gastro-oesophageal reflux disease) · Qualityof life

Large mixed para-oesophageal hernia accounts for only 5% of all hiatal hernias [1]. However, it can progress to massive proportion, leading to profound attenuation of diaphragmatic hiatus and volumetric displacement of anatomical structures within the thoracic cavity. Associated symptoms of para-oesophageal hernia include heartburn, dysphagia, regurgitation, atypical retrosternal chest pain, post-prandial chest discomfort, palpitations, early satiety and dyspnoea. The presence of para-oesophageal hernia generally implies great risk to the patient, as it is potentially associated with life-threatening complications including aspiration, haemorrhage, strangulation, volvulus and perforation [1, 2]. Most authorities advocate elective repair of symptomatic giant hiatal hernia [1–6]. Currently, laparoscopic repair is the accepted standard approach for surgical treatment for gastro-oesophageal reflux disease. It is a widely practised procedure for repair of para-oesophageal hernia for its perceived superior morbidity and mortality rate and short hospital stay [3, 4, 7, 8]. Published series from centres specialising in laparoscopic repair of hiatal hernia have consistently reported satisfactory outcomes [1–8].

We have observed that a significant proportion of patients with large hiatal hernia complain of increasing

J. C. Zhu · G. Becerril · K. Marasovic · G. L. Falk (✉)
Departments of Upper GI Surgery and Endosurgery, Concord Repatriation General Hospital, Sydney, NSW 2139, Australia
e-mail: glfalk1@gmail.com

A. J. Ing
Thoracic Medicine, Concord Repatriation General Hospital, Sydney, NSW, Australia

levels of dyspnoea over months to years prior to presentation. Post-operatively, these patients frequently report improvement or resolution of respiratory symptoms. The purpose of this paper is to examine the relationship between pulmonary function tests and severity of dyspnoea before and after laparoscopic repair of large intra-thoracic hiatal hernia. We wish to determine whether improvement of dyspnoea can be explained by an objective improvement in post-operative respiratory function tests. Patient symptomatic outcomes and quality of life before and after laparoscopic hiatal hernia repair were evaluated.

Patients and methods

From January 2004 to December 2008, 33 consecutive patients with large mixed and para-oesophageal hernia were included. All patients underwent laparoscopic repair and were followed up for a minimum of 2 years. Relevant clinical and treatment-related data of each patient were prospectively collected and maintained in a computerised database. Three patients were excluded from this study; Two patients had incomplete clinical data, and the other patient withdrew from the study. This study was approved by the Hospital Human Research Ethics Committee. Informed consent was obtained from each patient prior to commencement of their pre-operative work-up and surgery.

Pre-operative work-up

Pre-operatively, all symptoms relating to giant hiatal hernia were documented. Patients graded the symptoms of heartburn, retrosternal pain, dysphagia and regurgitation on a scale of 1–4 (1 = none, 2 = mild, 3 = moderate, 4 = severe) on a standard pro forma. For the purpose of this study, patients were asked to grade their dyspnoea by using a severity index (1 = no dyspnoea, 2 = dyspnoea with exertion, 3 = dyspnoea with basic activities, 4 = dyspnoea at rest). All patients underwent assessment in the form of barium meal, endoscopy and oesophageal manometry. Large, mixed or para-oesophageal hernia was defined as >50% of the stomach in the thoracic cavity. All patients underwent formal respiratory function tests within 1 week preceding the operation. These were performed according to American Thoracic Society criteria [9] and consisted of forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), full lung volumes including total lung capacity (TLC) and residual volume (RV). Reversibility of airway limitation was routinely tested in all patients with administration of bronchodilator aerosol. Increase in FEV1 >12% from baseline was considered to be significant.

Surgical technique

Laparoscopic giant mixed and para-oesophageal hernia repair involves dissection of the hernia sac from the mediastinum and restoring the hernia contents into the abdomen. Open cannulation laparoscopic five-port technique was utilised at our centre. The hernia sac and the gastro-oesophageal junction were widely mobilised with both vagus nerves identified and preserved. Upper short gastric vessels were routinely divided. A segment of intra-abdominal oesophagus was always achieved without tension by extensive proximal oesophageal mobilisation. Repair of the hiatus was performed by using Ethibond sutures posteriorly (0 Ethibond; Ethicon, Johnson and Johnson International, Brussels) and calibrated by insertion of a 56-French bougie. A short floppy fundoplication was performed in routine fashion. The fundoplication was then sutured to the crura of the diaphragm posteriorly to stabilise the wrap in the correct orientation and to maintain its sub-diaphragmatic position. The size of the hernia defect and the proportion of stomach herniating into the thoracic cavity were routinely recorded, according to both surgical and barium study findings.

Post-operative follow-up

Barium study was performed in the immediate post-operative phase before the patient was discharged to evaluate acute complications or early recurrence. The patients were reviewed in the surgeon's private room at 6 weeks, 3 months, 6 months and yearly thereafter. At each visit, review of symptomatic outcomes and systematic physical examination were conducted. The patient's gastro-oesophageal reflux disease (GERD) symptom severity as well as dyspnoea severity were graded on the standard pro forma. The patient had repeat barium swallow or gastroscopy routinely between 6 and 12 months post-operatively. Repeat respiratory function test was routinely performed prior to follow-up at 3–6 months after laparoscopic repair. All 30 enrolled patients completed post-operative respiratory function tests.

Quality-of-life assessment

Prior to operation and at each follow-up visit, the patient was asked to fill out a quality-of-life questionnaire. Quality of life was evaluated by means of the Gastrointestinal Quality of Life Index [10]. This questionnaire is a well-established quality-of-life assessment, validated and recommended by the European Study Group for Antireflux Surgery [10]. This questionnaire includes 36 items, the general responses being assigned values ranging from 0 to 144 points. The GIQLI is divided into five sub-categories

as follows: gastrointestinal symptoms (0–76 points), emotional status (0–28 points), physical function (0–28 points), social function and stress of medical treatment (0–4 points).

Statistical analysis

Clinical and treatment-related data of each patient were entered into a prospective computerised database (Microsoft Office Excel 2003). Clinical notes and charts of each patient were also retrieved for additional clinical parameters. All statistical analyses were performed using SPSS version 15.0.1 (SPSS Inc., Chicago, IL, USA). The paired Student *t*-test was utilised for comparison of continuous and normally distributed data; otherwise a nonparametric test in the form of a paired Wilcoxon rank test was used to compare means. *P*-values < 0.05 were regarded as significant.

Results

Patient characteristics

In the study period, 33 patients had laparoscopic giant hiatal hernia repair. Three patients were excluded from this study; Two patients had incomplete clinical data and one patient withdrew from the study. The 30 patients included in this study had complete post-operative follow-up of at least 2 years. There were 20 female patients, with mean and median age for the cohort being 70 (SD 10) years and 72 (range 44–88) years, respectively. Mean body height, weight and BMI were 161 (SD 8) cm, 76 (SD 10) kg and 29 (SD 2) kg/m^2, respectively. All patients had pre-operative endoscopy; four patients were found to have Barrett's mucosa, two patients had oesophageal ulcers and three patients had oesophagitis. All patients were on proton pump inhibitor therapy at the time of the study. All patients were referred for manometry study. Two manometry studies were abandoned due to poor patient tolerance. Manometry demonstrated reduced oesophageal peristalsis in 16 patients (53%). Intra-operatively, the mean size of hernia defect noted was 8 (SD 3) cm, while the mean proportion of the stomach herniated into the thoracic cavity was 73% (SD 5%). All patients had type II, III or IV hiatus hernia.

Mean post-operative hospital stay was 2.8 (SD 2) days. Overall morbidity for the patient cohort was 10%. There was no procedure-related mortality. One patient developed severe pneumonia with associated empyaemia that required intravenous (IV) antimicrobial therapy and thoracoscopy-guided decortication. Two patients developed food bolus impaction within 1 week of discharge despite provision of written dietary advice and required re-hospitalisation for endoscopic removal. Neither patient suffered further morbidity. On radiological follow-up, no patients had acute post-operative recurrence of hiatal hernia. Anatomical recurrence occurred in five patients (17%), demonstrated on follow-up barium study. Three were considered small (<2 cm in length), one was considered moderate (2–5 cm) and one large (>5 cm).

Symptomatic outcomes

The most common presenting symptoms included dyspnoea (87%), heartburn (60%), regurgitation (33%), retrosternal chest pain (53%) and dysphagia (50%). The absolute number of patients with symptoms and their associated mean and median severity scores pre and post laparoscopic hiatal hernia repair are outlined in Table 1. Pre-operatively, 26 patients (87%) presented with some degree of dyspnoea, and this number decreased to 4 patients (13%) after laparoscopic repair. Mean and median dyspnoea severity score decreased from 2.4 (SD 0.8) and 2.5 (range1–4) pre-operatively to 1.3 (SD 0.5) and 1 (range 1–3) post-operatively, respectively ($P < 0.001$).

Respiratory function test

The mean interval between pre-operative and post-operative respiratory test was 4.2 (SD 1.5) months. Pre-operatively, seven patients had significant airway obstruction on spirometric studies, defined as FEV1/FVC ratio <70%, suggesting co-morbid respiratory conditions. Three of these seven patients had reversible bronchial obstruction.

Compared with pre-operative results, no significant improvement was noted in post-operative FEV1, FVC, DLCO, TLC or RV values for the entire cohort (Table 2). Post-operatively, no patients developed new dyspnoea or complained of deterioration of their pre-operative dyspnoea. According to their pre-operative and post-operative dyspnoea severity indices, these 30 patients were further categorised into three groups: those who never complained of dyspnoea, those with resolution of dyspnoea and those who noted improvement but not complete resolution of dyspnoea after laparoscopic hiatal hernia repair. No significant post-operative improvement in FEV1, FVC, DLCO, TLC or RV values was noted in any of these three groups (Table 3).

Quality-of-life assessment

The pre-operative mean GIQLI score of 85.7 (SD 12.1) points was significantly improved to 107.9 (SD 9.2) points post-operatively ($P < 0.001$). This, however, did not reach the scores of the healthy individuals in our population control with GIQLI score of 118.2 (SD 8.7).

Table 1 Symptom outcomes

Symptoms	Pre-op., no.	Post-op., no.	Pre-op. SI, mean	Post-op. SI, mean	Post-op. SI, median	Post-op. SI, median	*P*-value
Heartburn	18 (60%)	5 (16%)	2.2	1.3	1	1	0.003
Chest pain	16 (53%)	2 (3%)	2.0	1.1	2.5	1	<0.001
Dysphagia	15 (50%)	2 (7%)	2.1	1.1	1.5	1.5	0.001
Regurgitation	10 (33%)	1 (3%)	1.7	1.0	1	1	0.005
Dyspnoea	26 (87%)	4 (13%)	2.4	1.3	2.5	1	<0.001

SI severity index

Table 2 Pre-operative and post-operative FEV1, FVC and DLCO values for the 30 patients with large hiatal hernia

Variable	Pre-op., mean	Post-op., mean	Improvement (%)	*P*-value
FEV1 (l)	2.03	2.08	1	0.148
FVC (l)	2.6	2.7	3	0.121
DLCO (ml/mmHg/min)	18.0	18.6	3	0.264
TLC (l)	4.8	4.9	2	0.393
RV (l)	2.0	1.9	–5	0.092

Table 3 Pre-operative and post-operative FEV1, FVC and DLCO values for the 30 patients divided into three groups according to dyspnoea response (n = number of patients)

Variable	Pre-op., mean	Post-op., mean	Improvement (%)	*P*-value
Patients with no initial dyspnoea ($n = 4$)				
FEV1 (l)	2.25	2.3	2	0.287
FVC (l)	2.65	2.75	4	0.187
DLCO (ml/mmHg/min)	21.3	20.4	–4	0.465
TLC (l)	5.1	5.2	2	0.254
RV (l)	2.3	2.3	0	0.912
Patients with dyspnoea improved ($n = 4$)				
FEV1 (l)	1.81	1.81	0	0.670
FVC (l)	2.1	2.2	4	0.114
DLCO (ml/mmHg/min)	15.7	16.3	4	0.439
TLV (l)	4.9	5.0	2	0.125
RV (l)	2.2	2.3	5	0.147
Patients with dyspnoea resolved ($n = 22$)				
FEV1 (l)	2.05	2.12	2	0.441
FVC (l)	2.54	2.62	4	0.09
DLCO (ml/mmHg/min)	19.2	20.1	3	0.537
TLC (l)	4.9	5.1	4	0.457
RV (l)	2.4	2.3	–5	0.314

Discussion

The relationship between respiratory symptoms and the presence of large hiatal hernia has been reported in a significant body of literature [11–17]. There are, however, few studies that assess the impact of large hiatal hernia repair on pulmonary function [18–20]. The potential mechanisms accounting for the presence of respiratory symptoms have not been clearly delineated.

Giant hiatal hernia in the form of either mixed or paraoesophageal hernia typically occurs in elderly patients with other associated medical co-morbidities. These patients usually report symptoms of dysphagia, regurgitation, postprandial chest pain, palpitations, early satiety and heartburn. A significant proportion of these patients also present with long-standing history of respiratory symptoms, predominantly in the form of dyspnoea, cough and wheeze. In this current series, pre-operative dyspnoea occurred in 87%

of patients with large hiatal hernia, this figure being perhaps slightly higher than rates reported in most series [11, 12, 14, 15, 21]. The higher incidence of dyspnoea detected in this study may be due to vigorous pre-operative and post-operative assessments and use of a standardised pro forma. Previous reports may have underestimated the incidence of dyspnoea as a presenting symptom of hiatal hernia by simply ascribing respiratory symptoms to patient's co-morbid medical conditions. Our patient population may have larger hiatus hernia than other reported series [11, 12, 14, 15, 21].

All patients noticed significant improvement in respiratory symptoms following hiatal hernia repair. This symptomatic improvement is confirmed by two studies by Low et al. and Senyk et al. that examined the relationship between hiatal hernia repair and pulmonary function [18–20]. In contrast to this study, however, Low et al. and Senyk et al. demonstrated that repair of para-oesophageal hernia could lead to a statistically significant improvement in spirometry values [18, 20]. Low et al. reported significant improvement in spirometry values in terms of mean FEV1 (pre-op., 1.87 l; post-op., 2.17 l; improvement, 16%; $P < 0.0001$) as well as mean forced vital capacity (FVC) (pre-op., 2.52 l; post-op., 2.89 l; improvement, 14.7%; $P < 0.0001$) in 45 patients who underwent open hiatal hernia repair [18]. Senyk et al. also demonstrated significant reduction of arterial oxygen tension in small hernia, and in vital capacity and maximal voluntary ventilation in medium-sized hernia [20]. A common spirometric finding detected by Senyk et al. in all their study subjects was significant increase in residual volume and wash-out volume following hiatal hernia repair [20]. The authors of these two studies suggested a variety of mechanisms to explain these spirometry findings [18–20].

The first mechanism suggested by these two studies is that, from a purely mechanical standpoint, impaired respiratory function could be due to compressive effect exerted by intra-cardiac hernia on pulmonary capacity and or volume [18–20]. Reduction of the herniated stomach or any associated viscera from the thoracic to the abdominal cavity restored normal chest anatomy and lung capacity and therefore led to improvement in overall respiratory function [18–20]. Presumably, the larger the volume of intra-thoracic hernia, the greater the expected improvement in respiratory function [18–20]. Low et al. correlated the improvement in spirometry values to the size of the hernia, with patients with hernia size <50% having 10.9% and 1.6% changes in FEV1 and FCV compared with patients with hernia size of 100%, who had 19.6% and 19.7% changes in FEV1 and FVC post-operatively [18].

Other potential mechanisms proposed by these two studies were that hiatal hernia repair involved restoring the diaphragm to its normal anatomical contour and function and so led to improvement in respiratory function [18–20]. The diaphragmatic defects associated with giant hiatal hernia could lead to impaired expansion of lungs and significant atelectasis that may potentiate poor respiratory function [18–20]. Senyk et al. found a correlation of lung volume, regional ventilation and perfusion abnormalities with the transverse diameter of the hernia [19]. They suggested that the herniated contents could compress the lung parenchyma and lead to regional ventilation and perfusion mismatch as a possible source of spirometry and arterial oxygen saturation abnormalities [19].

Surgical correction of gastro-oesophageal reflux disease alone can lead to improvement in associated respiratory symptoms. This does not necessarily depend on the type or size of the hiatal hernia. This phenomenon may be related to gastro-oesophageal reflux-induced bronchospasm caused by micro- or macro-aspirations [22]. The increased incidence of cough, asthma and pulmonary interstitial disease in patients with gastro-oesophageal reflux disease suggests that the presence of reflux may be a contributing factor to pre-operative dyspnoea [13, 22–24].

Regardless of mechanisms proposed by the previous studies, we did not demonstrate similar spirometry improvements, as suggested by Low et al. and Senyk et al., in our patients who underwent laparoscopic giant hiatal hernia repair. The mean dyspnoea index in our patients decreased from 2.4 to 1.3. This, however, was not accompanied by corresponding changes in pre- or post-operative FEV1, FVC, FEV1/FCV ratio, TLC or RV. This suggests that the mechanisms underlying dyspnoea may be much more complex than simple loss of lung volume, regional ventilation/perfusion mismatch, diaphragmatic dysfunction and/or bronchospasm.

Another potential cause of pre-operative dyspnoea associated with large hiatal hernia may be cardiac. Arrhythmia and heart failure have been previously reported in literature of large hiatal hernia [25–29]. Ito et al. reported severe exertional dyspnoea that resulted from large hiatal hernia that compressed the heart and led to ineffective respiration [28]. Kounis et al. showed that patients with hiatal hernia can have electrocardiographic alteration and increased central venous and pulmonary wedge pressures [29]. This report also demonstrated that the electrocardiographic alteration disappeared and the pressures returned to normal after correction of hiatal hernia [29]. The evidence examining cardiac failure as a cause of dyspnoea in the presence of large hiatal hernia is modest in current literature. Understanding of the ramifications of large hiatal hernia on cardiac function and respiration is limited.

During the past decade, laparoscopic fundoplication has largely replaced the open approach worldwide. Large studies have shown that laparoscopic hiatal hernia repair is

a safe and effective surgical procedure that provides good symptomatic relief and better functional outcome at medium- to long-term follow-up [1–5, 7]. In the present study, complications were minimal and there was no post-procedure mortality. The mean duration of hospital stay was also short. The dyspnoea severity index improved significantly, as did a wide range of symptoms including heartburn, chest pain, dysphagia and regurgitation. We demonstrated a dramatic improvement in quality of life. The pre-operative mean GIQLI score of 85.7 (SD 12.1) points was significantly lower in comparison with the post-operative GIQLI score of 107.9 (SD 9.2) points at 2-year follow-up. This is consistent with a number of large series that reported similar results. Wang et al., in a study of 231 patients who underwent laparoscopic anti-reflux surgery, reported a significant post-operative increase in GIQLI score from 99.3 to 110.0 points [30].

Conclusions

Patients with large hiatal hernia can frequently present with dyspnoea. Following laparoscopic hiatal hernia repair, improvement in dyspnoea and symptomatic outcomes occurs. Previous proposed mechanisms explaining the improvement in respiratory symptoms were thought to be related to compression of lung volume and resultant ventilation and perfusion mismatch. This current study is at variance with previous studies, as we did not detect a significant change in spirometry values of 30 patients who had laparoscopic large hiatal hernia repair. The improvement of their dyspnoeic sensation is, however, in accordance with previous reports. Our study raises the possibility that there is perhaps more to dyspnoea than localised lung volume loss alone. Given that previous work only showed very modest internal lung changes in blood flow and air flow in the compressed lung, an alternative mechanism to explain pre-operative shortness of breath should be sought. Cardiac dysfunction, in particular having more significant and global impact on pulmonary function, requires further consideration and examination as an aetiological mechanism.

Disclosures Authors Jacqui C. Zhu, Guillermo Becerril, Katy Marasovic, Alvin J. Ing and Gregory L. Falk have no conflicts of interest or financial ties to disclose.

References

1. Buenaventura PO, Schauer PR, Keenan RJ, Luketich JD (2000) Laparoscopic repair of giant paraesophageal hernia. Semin Thorac Cardiovasc Surg 12(3):179–185
2. Aly A, Munt J, Jamieson GG, Ludemann R, Devitt PG, Watson DI (2005) Laparoscopic repair of large hiatal hernias. Br J Surg 92(5):648–653
3. Andujar JJ, Papasavas PK, Birdas T, Robke J, Raftopoulos Y, Gagne DJ, Caushaj PF, Landreneau RJ, Keenan RJ (2004) Laparoscopic repair of large paraesophageal hernia is associated with a low incidence of recurrence and reoperation. Surg Endosc 18(3):444–447
4. Nason KS, Luketich JD, Qureshi I, Keeley S, Trainor S, Awais O, Shende M, Landreneau RJ, Jobe BA, Pennathur A (2008) Laparoscopic repair of giant paraesophageal hernia results in long-term patient satisfaction and a durable repair. J Gastrointest Surg 12(12):2066–2075 discussion 2075-2067
5. Pierre AF, Luketich JD, Fernando HC, Christie NA, Buenaventura PO, Litle VR, Schauer PR (2002) Results of laparoscopic repair of giant paraesophageal hernias: 200 consecutive patients. Ann Thorac Surg 74(6):1909–1915 discussion 1915-1906
6. Wolf PS, Oelschlager BK (2007) Laparoscopic paraesophageal hernia repair. Adv Surg 41:199–210
7. Khaitan L, Houston H, Sharp K, Holzman M, Richards W (2002) Laparoscopic paraesophageal hernia repair has an acceptable recurrence rate. Am Surg 68(6):546–551 discussion 551-542
8. Targarona EM, Novell J, Vela S, Cerdan G, Bendahan G, Torrubia S, Kobus C, Rebasa P, Balague C, Garriga J, Trias M (2004) Mid term analysis of safety and quality of life after the laparoscopic repair of paraesophageal hiatal hernia. Surg Endosc 18(7):1045–1050
9. Society AT (1994) Standardization of Spirometry. http://www thoracicorg/sections/publications/statements/pages/archive/201 html. Accessed 17 June 2009
10. Korolija D, Sauerland S, Wood-Dauphinee S, Abbou CC, Eypasch E, Caballero MG, Lumsden MA, Millat B, Monson JR, Nilsson G, Pointner R, Schwenk W, Shamiyeh A, Szold A, Targarona E, Ure B, Neugebauer E (2004) Evaluation of quality of life after laparoscopic surgery: evidence-based guidelines of the European Association for Endoscopic Surgery. Surg Endosc 18(6):879–897
11. Champion GL, Richter JE (1993) Atypical presentation of gastroesophageal reflux disease: chest pain, pulmonary, and ear, nose, throat manifestations. Gastroenterologist 1(1):18–33
12. Frye JW, Vaezi MF (2008) Extraesophageal GERD. Gastroenterol Clin North Am 37(4):845–858, ix
13. Greub G, Liaudet L, Wiesel P, Bettschart V, Schaller MD (2003) Respiratory complications of gastroesophageal reflux associated with paraesophageal hiatal hernia. J Clin Gastroenterol 37(2):129–131
14. Gurski RR, da Rosa AR, do Valle E, de Borba MA, Valiati AA (2006) Extraesophageal manifestations of gastroesophageal reflux disease. J Bras Pneumol 32(2):150–160
15. Napierkowski J, Wong RK (2003) Extraesophageal manifestations of GERD. Am J Med Sci 326(5):285–299
16. Selmonosky CA, Blanc JS, Byrd R (1980) Hiatal hernia and pulmonary function impairment: incidence or coincidence? South Med J 73(9):1234–1236
17. Sontag SJ (2005) The spectrum of pulmonary symptoms due to gastroesophageal reflux. Thorac Surg Clin 15(3):353–368
18. Low DE, Simchuk EJ (2002) Effect of paraesophageal hernia repair on pulmonary function. Ann Thorac Surg 74(2):333–337 discussion 337
19. Senyk J, Arborelius M Jr, Lilja B (1975) Respiratory function in esophageal hiatus hernia. II. Regional lung function. Respiration 32(2):103–111
20. Senyk J, Arborelius M Jr, Lilja B, Ohlsson NM (1975) Respiratory function in esophageal hiatus hernia. I. Spirometry, gas distribution, and arterial blood gases. Respiration 32(2):93–102

21. Richter JE (2000) Extraesophageal presentations of gastroesophageal reflux disease: an overview. Am J Gastroenterol 95(8 Suppl):S1–S3
22. Harding SM, Schan CA, Guzzo MR, Alexander RW, Bradley LA, Richter JE (1995) Gastroesophageal reflux-induced bronchoconstriction. Is microaspiration a factor? Chest 108(5):1220–1227
23. Vincent D, Cohen-Jonathan AM, Leport J, Merrouche M, Geronimi A, Pradalier A, Soule JC (1997) Gastro-oesophageal reflux prevalence and relationship with bronchial reactivity in asthma. Eur Respir J 10(10):2255–2259
24. Kiljander TO, Salomaa ER, Hietanen EK, Ovaska J, Helenius H, Liippo K (2002) Gastroesophageal reflux and bronchial responsiveness: correlation and the effect of fundoplication. Respiration 69(5):434–439
25. Devbhandari MP, Khan MA, Hooper TL (2007) Cardiac compression following cardiac surgery due to unrecognised hiatus hernia. Eur J Cardiothorac Surg 32(5):813–815
26. Hokamaki J, Kawano H, Miyamoto S, Sugiyama S, Fukushima R, Sakamoto T, Yoshimura M, Ogawa H (2005) Dynamic electrocardiographic changes due to cardiac compression by a giant hiatal hernia. Intern Med 44(2):136–140
27. Hunt GS, Gilchrist DM, Hirji MK (1996) Cardiac compression and decompensation due to hiatus hernia. Can J Cardiol 12(3):295–296
28. Ito H, Kitami M, Ohgi S, Ohe H, Ozoe A, Sasaki H, Konnai T (2003) Large hiatus hernia compressing the heart and impairing the respiratory function: a case report. J Cardiol 41(1):29–34
29. Kounis NG, Zavras GM, Kitrou MP, Soufras GD, Constantinidis K (1988) Unusual electrocardiographic manifestations in conditions with increased intrathoracic pressure. Acta Cardiol 43(6):653–661
30. Wang W, Huang MT, Wei PL, Lee WJ (2008) Laparoscopic antireflux surgery for the elderly: a surgical and quality-of-life study. Surg Today 38(4):305–310

OESOPHAGEAL CARCINOMA

I developed an innovative interest in the curative surgical management of oesophageal carcinoma from the inception of my practice as a senior surgeon. During this period, I initially introduced minimally invasive surgery for oesophagectomy but at the same time more radical surgery was being evaluated with extensive resection within the chest of the oesophagus and peri oesophageal tissues as well as an extensive lymph node removal (lymphadenectomy). Also spoke at many meetings regarding MIS oesophagectomy and trained surgeons in the technique in the mid-1990s, my pursuit was more in the curability of oesophageal cancer and the post-operative care of the patient with a view to minimal complicated recovery, reducing the anastomotic leak rate. To that purpose I became involved in some basic research which led to one of the first publications on magnetic resonance spectroscopy in Barrett's oesophagus and adenocarcinoma of the oesophagus which then was hugely increasing in frequency. This disease was thought to be due to reflux, leading to several animal studies one of which was published and the others subject of presentation and abstracts. We evaluated surgical cure against the extent of lymphadenectomy and also was somewhat perplexed by the lack of evidence for neoadjuvant chemotherapy, which has subsequently also been evident in the Karolinska population database study from Sweden. All this was achieved with more radical surgical procedure with a very high level of surgical cure quite evident in our initial publication by Martin at al. Further demonstration of the effectiveness of lymphadenectomy was published in Annals of Oncology by Clive Kelty.

During this period diagnosis and staging of oesophageal carcinoma was very important in establishing therapeutic alternatives. The new technology of endoscopic ultrasound offered the prospect of being able to identify small lymph nodes containing carcinoma alongside the oesophagus. Our group therefore purchased the first instrument in Australia and published the first clinical experience of endoscopic ultrasound in staging of oesophageal carcinoma. Whilst being highly effective in identifying positive lymph nodes, it was relatively poor at assessing resectability of the lesion due to the lack of ability of the ultrasound to demonstrate invasion of mediastinal structures.

This test remains as useful today in the staging of oesophageal carcinoma.

I convened the QIMR New South Wales component of the Australian cancer study into carcinoma of the oesophagus, setting up the Sydney office at Repatriation Gen Hospital Concord. Hospital staff supplied, and contributed the largest group of patients outside of Queensland to this study which led to more than 10 publications on a collaborative basis.

I further developed a novel technique for managing post-operative discomfort and improved patient outcome leading to diminished length of stay in intensive care, less hypotension and less post- thoracotomy pain. This technique is now being utilised around the world at many sites by my international trainees, as they took up consultant positions. Many of these sites have achieved world recognition for oesophageal cancer surgery. Furthermore appopriate surgical post-operative care has improved to the extent that very aged patients could have curative treatment without major mortality, a series published by Dr J Park as part of a PhD candidature at Notre Dame University, Sydney.

References:

1. Park JS, Van der Wall H, Kennedy CW, Falk GL. Does age affect oesophagectomy survival: a cohort study. ANZ J Surg. 2021;91(1-2):E14-e9.

2. Barbour AP, Walpole ET, Mai GT, Barnes EH, Watson DI, Ackland SP, et al. Preoperative cisplatin, fluorouracil, and docetaxel with or without radiotherapy after poor early response to cisplatin and fluorouracil for resectable oesophageal adenocarcinoma (AGITG DOCTOR): results from a multicentre, randomised controlled phase II trial. Ann Oncol. 2020;31(2):236-45.

3. Rai R, Notaras A, Corke P, Falk GL. Regional pain management for oesophagectomy: Cohort study suggests a viable alternative to a thoracic epidural to enhance recovery after surgery. European Surgery. 2020;52(1):22-8.

4. Mitchell DP, Yeluri S, Van der Wall H, Falk GL. The real risk of nodal disease in T1 oesophageal adenocarcinoma. European Surgery. 2020;52(3):110-7.

5. Phillips S, Dedic-Hagan J, Baxter dAF, Van der Wall H, Falk GL. A Novel Technique of Paravertebral Thoracic and Preperitoneal Analgesia Enhances Early Recovery After Oesophagectomy. World Journal of Surgery. 2018;42(6):1787-91.

6. Atie M, Dunn G, Falk GL. Chlyous leak after radical oesophagectomy: Thoracic duct lymphangiography and embolisation (TDE)—A case report. International Journal of Surgery Case Reports. 2016;23:12-6.

7. Brown T, D'Netto TJ, Falk GL, Phillips S. Paravertebral Catheter Placement, Under Direct Vision, for Postthoracotomy Analgesia. Surg Laparosc Endosc Percutan Tech. 2015;25(6):e170-1.

8. Smithers BM, Fahey, P.P., Corish, T., Gotley, D.C., Falk, G.L., Smith, G.S., Kiroff, G.K., Clouston, A.D., Watson, D.I., Whiteman, D.C. Symptoms, investigation and management of patients with cancer of the oesophagus and gastro-oesophageal junction in Austalia. The Medical Journal of Australia. 2010;193(10):572-7.

9. Kelty CJ, Kennedy CW, Falk GL. Ratio of metastatic lymph nodes to total number of nodes resected is prognostic for survival in esophageal carcinoma. J Thorac Oncol. 2010;5(9):1467-71.

10. Martin DJ, Church NG, Kennedy CW, Falk GL. Does systematic 2-field lymphadenectomy for esophageal malignancy offer a survival advantage? Results from 178 consecutive patients. Dis Esophagus. 2008;21(7):612-8.

11. Doran ST, Falk GL, Somorjai RL, Lean CL, Himmelreich U, Philips J, et al. Pathology of Barrett's esophagus by proton magnetic resonance spectroscopy and a statistical classification strategy. Am J Surg. 2003;185(3):232-8.

12. Moore KH, Barry P, Burn J, Falk G. Adenocarcinoma of the rat esophagus in the presence of a proton pump inhibitor: a pilot study. Dis Esophagus. 2001;14(1):17-22.

13. Pham T, Roach E, Falk GL, Chu J, Ngu MC, Jones DB. Staging of oesophageal carcinoma by endoscopic ultrasound: preliminary experience. Aust N Z J Surg. 1998;68(3):209-12.

14. MacLeod C, Moylan E, Falk GL. Carcinoma of the esophagus treated with radical chemoradiation 19 years after irradiation for recurrent breast cancer. Dis Esophagus. 1997;10(2):145-8.

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

Preoperative cisplatin, fluorouracil, and docetaxel with or without radiotherapy after poor early response to cisplatin and fluorouracil for resectable oesophageal adenocarcinoma (AGITG DOCTOR): results from a multicentre, randomised controlled phase II trial

A. P. Barbour[1,2*], E. T. Walpole[1], G. T. Mai[1], E. H. Barnes[3], D. I. Watson[4,5], S. P. Ackland[6], J. M. Martin[6], M. Burge[2,7], R. Finch[7], C. S. Karapetis[4,5], J. Shannon[8], L. M. Nott[9], S. Varma[10], G. Marx[11], G. L. Falk[11], V. Gebski[3], M. Oostendorp[3], K. Wilson[3], J. Thomas[1,12], G. Lampe[1], J. R. Zalcberg[13], J. Simes[3] & B. M. Smithers[1,2], on behalf of the DOCTOR investigators†

[1]Divisions of Surgery and Cancer Services, Princess Alexandra Hospital; [2]Faculty of Medicine, The University of Queensland, Brisbane; [3]National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney; [4]Department of Surgery, Flinders Medical Centre; [5]School of Medicine, Flinders University, Adelaide; [6]School of Medicine and Public Health, University of Newcastle, Newcastle; [7]Cancer Care Services, Royal Brisbane and Women's Hospital, Brisbane; [8]Nepean Cancer Centre, Nepean Hospital, Sydney; [9]Medical Oncology, Royal Hobart Hospital, Hobart; [10]Cancer Services, Townsville Hospital, Townsville; [11]Clinical Trials Unit, Sydney Adventist Hospital, Sydney; [12]Clinical Trials, Mater Research Institute, Brisbane; [13]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia

Available online 6 January 2020

Background: Patients with oesophageal/gastro-oesophageal junction adenocarcinoma (EAC) not showing early metabolic response (EMR) to chemotherapy have poorer survival and histological response rates <5%. We investigated whether tailoring neoadjuvant therapy can improve outcomes in these patients.

Patients and methods: Patients with resectable EAC were enrolled and randomised into two single-arm, multicentre phase II trials. After induction cisplatin and 5-fluorouracil (CF), all were assessed by day 15 positron emission tomography (PET). Patients with an EMR [maximum standardised uptake values (SUVmax) ≥35% reduction from baseline to day 15 PET] received a second CF cycle then oesophagectomy. Non-responders were randomised 1 : 1 to two cycles of CF and docetaxel (DCF, $n = 31$) or DCF + 45 Gy radiotherapy (DCFRT, $n = 35$) then oesophagectomy. The primary end point was major histological response (<10% residual tumour) in the oesophagectomy specimen; secondary end points were overall survival (OS), progression-free survival (PFS), and locoregional recurrence (LR).

Results: Of 124 patients recruited, major histological response was achieved in 3/45 (7%) with EMR, 6/30 (20%) DCF, and 22/35 (63%) DCFRT patients. Grade 3/4 toxicities occurred in 12/45 (27%) EMR (CF), 13/31 (42%) DCF, and 25/35 (71%) DCFRT patients. No treatment-related deaths occurred. LR by 3 years was seen in 5/45 (11%) EMR, 10/31 (32%) DCF, and 4/35 (11%) DCFRT patients. PFS [95% confidence interval (CI)] at 36 months was 47% (31% to 61%) for EMR, 29% (15% to 45%) for DCF, and 46% (29% to 61%) for DCFRT patients. OS (95% CI) at 60 months was 53% (37% to 67%) for EMR, 31% (16% to 48%) for DCF, and 46% (29% to 61%) for DCFRT patients.

Conclusions: EMR is associated with favourable OS, PFS, and low LR. For non-responders, the addition of docetaxel augmented histological response rates, but OS, PFS, and LR remained inferior compared with responders. DCFRT improved histological response and PFS/LR outcomes, matching the EMR group. Early PET/CT has the potential to tailor therapy for patients not showing an early response to chemotherapy.

Trial registration: ACTRN12609000665235.

Key words: chemotherapy, gastro-oesophageal junction adenocarcinoma, metabolic response, neoadjuvant therapy, oesophageal adenocarcinoma

INTRODUCTION

Surgery with preoperative chemotherapy or chemo-radiotherapy is standard of care for potentially curable oesophageal and gastro-oesophageal junction adenocarcinoma (EAC) patients.[1,2] At the time of study conception, cisplatin and 5-fluorouracil (CF)-based chemo- or chemo-radiotherapy were standards of care. Current treatment options include perioperative docetaxel, oxaliplatin, and

*Correspondence to: Prof. Andrew P. Barbour, Diamantina Institute, University of Queensland, Translational Research Institute & Princess Alexandra Hospital, 37 Kent St, Woolloongabba, QLD 4012, Australia. Tel: +61-738477133
E-mail: a.barbour@uq.edu.au (A. P. Barbour).

†See Acknowledgements for full list of DOCTOR investigators.

5-fluorouracil (FLOT4) chemotherapy,[3,4] preoperative CF chemotherapy[2,5] or chemoradiotherapy, and carboplatin and paclitaxel (CP)-based chemoradiotherapy.[6] The role of preoperative radiotherapy (RT) is still debatable.[1,5,7–12] All these options and combinations are acceptable standards of care for EAC in international guidelines.[13–15]

Histological response and residual nodal disease are prognostic factors,[16–20] but are assessed *after* preoperative therapy and resection. In a prospective study, Ott et al.[21] compared maximum standardised uptake values (SUVmax) of [^{18}F]2-fluoro-2-deoxy-D-glucose (^{18}FDG)-positron emission tomography (PET) before chemotherapy and on day 14 (d14) after the first cycle of treatment ('early metabolic response'; EMR). A ≥35% reduction in SUVmax predicted major histological response and a better progression-free survival (PFS) after resection.[21] Similar survival outcomes were demonstrated in MUNICON I,[22] where patients with adenocarcinoma and EMR to the first cycle of CF-based chemotherapy received up to 12 weeks of chemotherapy then resection, while metabolic non-responders went directly to surgery.[21] In MUNICON II,[23] those exhibiting metabolic non-response received radiation therapy, with the same chemotherapy. Although the histopathologic response rate increased from <5% to 20%, there was no improvement in survival. It remains uncertain whether any change in therapy to improve histopathologic response will translate into improved survival.

We report a randomised, non-comparative phase II trial to determine whether adding docetaxel to CF chemotherapy (DCF), with or without RT, can significantly improve the major histological response rates in patients with metabolic non-response compared with historical outcomes reported by Ott et al.[21] if the same chemotherapy had been continued (expected to be <5%). Our hypothesis was that identifying metabolic non-response early may allow a change in systemic cancer management to improve histologic response and patient survival.

METHODS

Patient characteristics

Participants had biopsy-proven, localised resectable EAC, including Siewert type I and type II disease. Eligibility criteria included T2 or T3 stage[24] based on a computed tomography (CT) scan and in some instances, endoscopic ultrasound, T1b with poor differentiation or T1N1+, and a primary tumour sufficiently FDG-avid (minimum SUVmax 3.5). Patients were excluded if they had a tumour located in the cervical oesophagus or stomach (i.e. Siewert type III), metastatic disease, or a history of radiation therapy to the chest, prior chemotherapy, or another malignancy within the last 5 years.

The study was carried out in accordance with the Declaration of Helsinki. Central and institutional ethics and local research governance approval was required, and all patients were ≥18 years old and provided written informed consent. Participants were recruited from seven sites across Australia.

Study design

The study was designed as two single-arm, multicentre, prospective, randomised exploratory phase II trials (Figure 1). Metabolic response was assessed by ^{18}FDG-PET/CT scans before treatment and on d15 after the start of chemotherapy. The responders (defined by a mean SUV decrease ≥35%[21,22]) proceeded to a second cycle of the same chemotherapy and then to surgery; non-responders were centrally randomised to DCF or DCF + 45 Gy radiotherapy (DCFRT) between d15 and d21. Treatment allocation was stratified by tumour site (oesophagogastric junction versus oesophagus) and hospital site, and randomisation used the minimisation method. DOCTOR is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12609000665235).

PET scans

Baseline and d15 ^{18}FDG-PET scans were carried out on the same scanner with identical ^{18}FDG dose and uptake time. Scans included a low-dose CT from the base of the skull to mid-thigh for attenuation correction (see supplementary material, available at *Annals of Oncology* online).

Chemotherapy

All patients received standard CF chemotherapy. For the EMR group, CF was repeated on d22 and followed by oesophagectomy. The metabolic non-responder group were randomised 1 : 1 to DCF chemotherapy (arm A) or DCFRT (arm B); full details are given in the supplementary material, available at *Annals of Oncology* online.

Radiation therapy

Radiation therapy commenced on d22. Target volume included primary and nodal disease, with the clinical target volume of 0.5 cm radially and 3 cm craniocaudally along the line of the oesophagus. The total dose was 45 Gy at 1.8 Gy per fraction, once daily, 5 days/week, in 25 fractions. Conformal planning with tissue inhomogeneity correction was required for all patients.

Restaging and surgery

Restaging with endoscopy and CT scans was carried out after the second cycle of CF for the responders and after completion of DCF with/without RT for randomised patients. Surgery was to be 6 weeks (±2 weeks) after completion of preoperative therapy (details in the supplementary material, available at *Annals of Oncology* online).

Histopathology

The primary tumour response to neoadjuvant therapy was reported as the percentage of residual viable tumour cells compared with fibrotic stroma[16,22–23,25] with differentiation between a major histological response (<10% residual viable tumour cells, including complete responses with no viable tumour cells) and a minor response (≥10% residual viable tumour cells). Proximal and distal resection margins >5 mm and circumferential resection margins defined as

https://doi.org/10.1016/j.annonc.2019.10.019

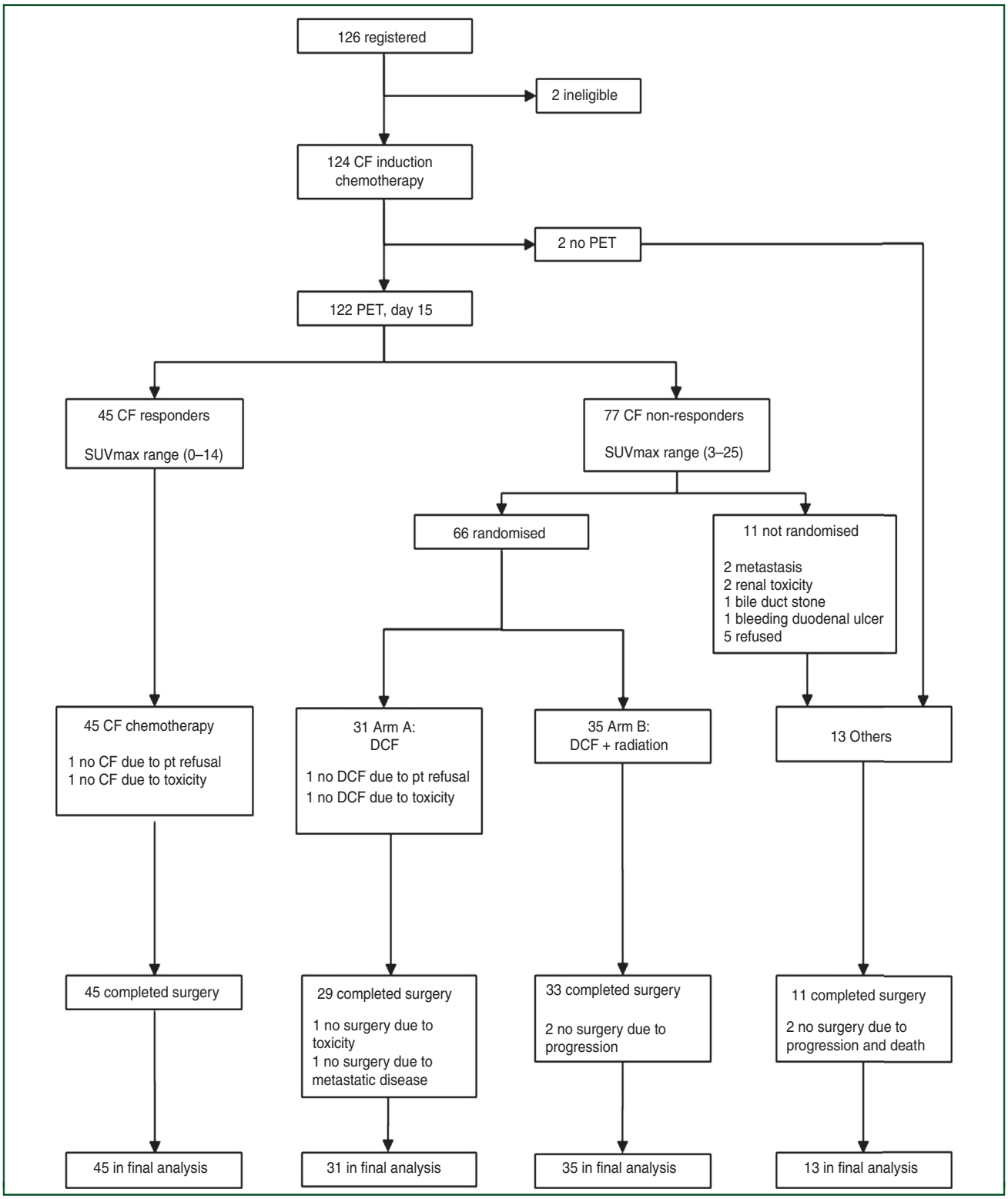


Figure 1. Study design and patient flow.
CF, cisplatin and 5-fluorouracil chemotherapy; DCF, docetaxel, cisplatin, and 5-fluorouracil (modified CF chemotherapy); PET, positron emission tomography; SUVmax, maximum standardised uptake values.

viable tumour cells $\geq$1 mm from the resection margin were considered R0 (microscopically clear).

Follow-up

Patients had a clinical assessment every 3 months in the first 2 years, and 6-monthly for the next 3 years. CT scans of the chest and abdomen were done every 6 months for the first 2 years and then annually for 3 years. Otherwise, investigations were directed as clinically indicated.

Recurrence

Locoregional recurrence (LR) was defined as disease involving the primary tumour site or locoregional lymph

nodes, including the coeliac trunk or supraclavicular region. All other sites of recurrence were considered distant.[26]

End points and statistics

The study was designed as two single-arm phase II studies of PET non-responders to standard CF chemotherapy, with an expected major histological response rate of <5%, based on Ott et al.[21] and MUNICON I.[22] The primary end point was major histological response, with a response rate of at least 20% in either arm being of clinical interest. Power was calculated on the basis of Simon's two-stage design: a sample of 30 subjects per study would have 80% power with 95% confidence to rule out a response rate of 5% or less if the true response rate was 20% or higher.

Preplanned secondary end points were PFS at 3 years and overall survival (OS) at 5 years (measured from the date of randomisation), grade 3 or 4 toxicities from DCF or radiation therapy (as measured by National Cancer Institute Common Toxicity Criteria Version 3.0), and the proportion of patients with an EMR to one cycle of CF. Confidence intervals (CIs) for proportions were calculated using the Wilson method.

The decision to publish 3-year PFS and 5-year OS was based on consideration of data maturity[27] and because the percentage of full information in all study groups was at least 89%. Time-to-event outcomes were described using the Kaplan–Meier method and exploratory comparisons carried out using Cox proportional hazards regressions. All analyses used SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients

From 8 July 2009 until 29 December 2015, 126 patients were registered. Two were ineligible, so 124 patients (14 women, 110 men) had induction CF (Figure 1). The median age was 63 (range 38–78 years). Ninety patients (73%) had thoracic oesophageal or Siewert type I tumours, and 34 (27%) had Siewert type II tumours. The majority (81%) were clinically International Union Against Cancer (UICC) stage III (Table 1).

Metabolic response and randomisation

EMR was assessed on d15 (mean 13.9, range 12–20 days after starting chemotherapy) in 122 patients: 45 (37%; 95% CI, 29% to 46%) were responders and 77 (63%; 95% CI, 54% to 71%) were metabolic non-responders. Two patients were medically unfit for d15 ^{18}FDG-PET scans. The baseline characteristics were similar between responders and non-responders (Table 1). Of the 77 confirmed non-responders, 66 entered the randomisation phase: 31 were randomised to arm A (DCF) and 35 to arm B (DCFRT) (Figure 1).

Preoperative chemotherapy toxicity

Fifty-eight patients received at least one cycle of preoperative CF alone: 45 responders, the 11 metabolic non-responders who were not randomised (Figure 1), and the two patients who did not undergo d15 PET scans. Grade 3 or 4 adverse events occurred in 16/58 (28%) (supplementary material, Table S1, available at *Annals of Oncology* online).

The median docetaxel doses, dose modifications and omissions for arms A and B are detailed in the supplementary material (Results), available at *Annals of Oncology* online. Grade 3 or 4 adverse events occurred in 13/31 (42%) patients in arm A and 25/35 (71%) patients in arm B (supplementary Table S1). All patients in arm B received 45 Gy in 25 fractions starting on d22; one patient had a 3 day break during treatment but received all 25 fractions (45 Gy) of radiation therapy.

Surgery

Of 124 eligible patients, 118 (95%) underwent surgical resection: all 45 EMR; 29 in arm A; 33 in arm B; and 11 of the other patients underwent resection. One patient in arm A did not undergo resection due to DCF toxicity; one patient in arm A, two patients in arm B and two of the other patients did not undergo resection owing to distant tumour

Table 1. Baseline characteristics[a]

Characteristic	PET responders: CF (N = 45)	PET non-responders randomised: DCF (N = 31)	PET non-responders randomised: DCF + radiation (N = 35)	Others (N = 13)	All patients (N = 124)
Age (years), median (range)	61 (42–78)	60 (38–77)	63 (44–76)	65 (41–71)	63 (38–78)
Male	41 (91)	27 (87)	32 (91)	10 (77)	110 (89)
ECOG 0	37 (82)	25 (81)	27 (77)	13 (100)	102 (82)
Tumour site intrathoracic	27 (60)	21 (68)	21 (60)	8 (62)	77 (62)
Siewert type I	6 (33)	2 (20)	4 (29)	1 (20)	13 (28)
Siewert type II	12 (67)	8 (80)	10 (71)	4 (80)	34 (72)
Clinical UICC stage					
IB	7 (16)	4 (13)	3 (9)	1 (8)	15 (12)
IIA	4 (9)	2 (6)	1 (3)	1 (8)	8 (6)
IIB	20 (44)	16 (52)	23 (66)	8 (62)	67 (54)
IIIA	14 (31)	8 (26)	6 (17)	3 (23)	31 (25)
IIIB		1 (3)	2 (6)		3 (2)
Length of tumour (cm), median (range)	4.0 (0.7–10.0)	5.0 (0.3–11.0)	5.0 (0.7–10.0)	4.0 (2.0–10.0)	4.0 (0.3–11.0)

CF, cisplatin and 5-fluorouracil chemotherapy; DCF, docetaxel, cisplatin, and 5-fluorouracil (modified CF chemotherapy); ECOG, Eastern Cooperative Oncology Group performance status.

[a] Values are *n* (%) unless otherwise indicated.

progression (supplementary material, Table S2, available at *Annals of Oncology* online). There were three deaths within 90 days of surgery: one postoperative multiorgan failure (PET responder); two deaths from cancer (one arm A and one non-randomised non-responder). Surgical complications are shown in supplementary material, Table S3, available at *Annals of Oncology* online.

Primary tumour response and histopathology

Primary tumour response analysis was carried out in 123 patients (45 responders, 30 arm A, 35 arm B and 13 others) (Table 2). This included 118 who had resection and five who did not undergo surgery due to tumour progression (one in arm A, two in arm B, and two in the non-randomised metabolic non-responder group), as they were considered to have minor histopathologic responses. A sixth patient (arm A) who did not undergo surgery due to DCF toxicity was excluded from the primary tumour response analysis.

Major histological response was seen in 3/45 of the EMR group (7%; 95% CI, 2% to 18%) and 0/13 of the patients who had no d15 PET ($n = 2$) or were non-responders who were not randomised ($n = 11$). In arm A, 6/30 patients (20%; 95% CI, 10% to 37%) achieved major histological response and in arm B, 22/35 patients (63%; 95% CI, 46% to 77%) achieved major histological response. Of the 118 patients who had surgery, 91 (77%) had tumour-free resection margins (R0 resection) (Table 2).

PFS and patterns of recurrence

At 36 months since the last patient's surgery, median follow-up for the surviving patients was 62 months (95% CI 60% to 64%). Three-year PFS was 47% (95% CI 31% to 61%) in the EMR patients, 29% (95% CI 15% to 45%) for arm A, and 46% (95% CI 29% to 61%) for arm B (Figure 2A and Table 3). The remaining patients ($n = 13$) showed 3-year PFS of 37% (95% CI 13% to 62%) with median PFS 13 months (95% CI 5% to not releasable [NR]). Median PFS was 27 months (95% CI 12% to NR) for EMR patients, 22 months (95% CI 14% to 27%) for arm A, and 22 (95% CI 14% to NR) months for arm B.

Recurrent disease was documented in 78/124 (63%) patients (Table 3). For the EMR group, distant (18/45, 40%, 95% CI 23% to 50%) or combined LR and distant recurrence (2/45, 4%, 95% CI 1% to 15%) were most common, with

Table 2. Histopathology and tumour stage after neoadjvant treatment and surgery according to early metabolic response on PET (where data available)[a]

Characteristic	PET responders ($N = 45$)	PET non-responders randomised: DCF ($N = 29$)	PET non-responders randomised: DCF + radiation ($N = 33$)	Others ($N = 11$)	All patients ($N = 118$)
Primary tumour response					
Major[b] (<10% residual tumour)	3 (7)	6 (21)	22 (67)	0 (0)	31 (26)
Minor	42 (93)	23 (79)	11 (33)	11 (100)	87 (74)
ypT stage					
TX			1 (3)		1 (1)
T0		2 (7)	7 (21)		9 (8)
Tis			1 (3)		1 (1)
T1a	1 (2)		2 (6)		3 (3)
T1b	10 (22)	3 (10)	5 (15)	1 (9)	19 (16)
T2	8 (18)	4 (14)	5 (15)	1 (9)	18 (15)
T3	26 (58)	19 (66)	11 (33)	9 (82)	65 (55)
T4a		1 (3)	1 (3)		2 (2)
ypN stage					
NX	1 (2)		2 (6)		3 (3)
N0	18 (40)	13 (45)	19 (58)	3 (27)	53 (45)
N1	10 (22)	7 (24)	8 (24)	3 (27)	28 (24)
N2	11 (24)	3 (10)	4 (12)	1 (9)	19 (16)
N3	5 (11)	6 (21)		4 (36)	15 (13)
Number of lymph nodes examined, median (range)	25 (6–46)	27 (14–48)	21 (5–58)	31 (17–58)	24 (5–58)
Number of positive lymph nodes, median (range)	1 (0–18)	2 (0–16)	0 (0–14)	1 (0–15)	1 (0–18)
Differentiation					
Unknown		1 (3)	1 (3)		2 (2)
No tumour seen		2 (7)	8 (24)		10 (8)
Well differentiated	3 (7)	1 (3)	4 (12)		8 (7)
Moderately differentiated	12 (27)	5 (17)	13 (39)	5 (45)	35 (30)
Poorly differentiated	30 (67)	20 (69)	7 (21)	6 (55)	63 (53)
Vascular invasion present	24 (53)	11 (38)	3 (9)	4 (36)	42 (36)
Resection margins					
R0	33 (73)	18 (62)	31 (94)	9 (82)	91 (77)
R1[c]	12 (27)	11 (38)	2 (6)	2 (18)	27 (23)

DCF, docetaxel, cisplatin, and 5-fluorouracil; PET, positron emission tomography.

[a] Values are *n* (%) unless otherwise indicated.

[b] Complete pathological responses were seen in 1/46 (2%) PET responders, 2/29 (7%) randomised to DCF, and 8/33 (24%) randomised to DCF + radiation.

[c] Macroscopically clear resection but microscopically positive margins.

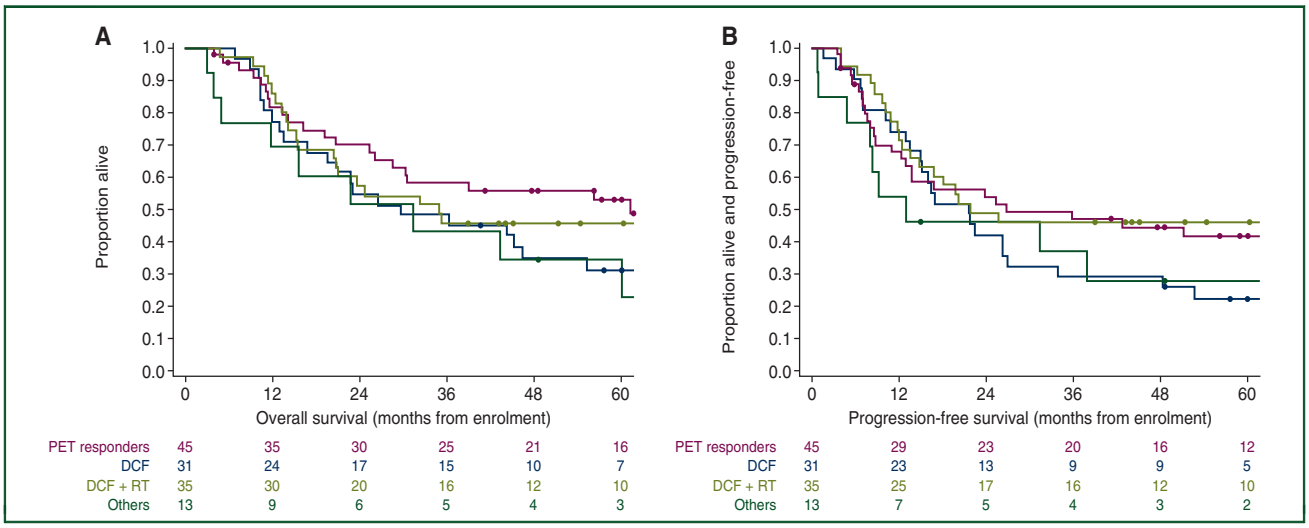


Figure 2. Kaplan-Meier plots of progression-free survival (A) and overall survival (B).
DCF, docetaxel, cisplatin, and 5-fluorouracil; PET, positron emission tomography; RT, radiotherapy.

3/45 (7%, 95% CI 2% to 18%) having isolated LR. Similarly, for arm B, distant recurrence was most common (15/35 patients, 43%, 95% CI 28% to 59%), followed by combined LR and distant recurrence (1/35, 3%, 95% CI 0.5% to 15%), and isolated LR (3/35 patients, 9%, 95% CI 3% to 23%). In contrast, patients in arm A more commonly developed isolated locoregional progression or LR (7/31 patients, 23%, 95% CI 14% to 43%) or LR and distant recurrence (2/31 patients, 6%, 95% CI 2% to 21%) compared with distant recurrence (10/31 patients, 32%, 95% CI 11% to 40%).

OS

Five-year OS was: EMR, 53% (95% CI 37% to 67%); arm A, 31% (95% CI 16% to 48%); arm B 46% (95% CI 29% to 61%) (Figure 2B); and the remaining patients ($n = 13$), 35% (95% CI 11% to 60%). Median OS was: EMR, 61 (95% CI 21% to NR) months; arm A, 30 (95% CI 17% to 55) months, and arm B, 35 (95% CI 20% to NR) (Table 3).

DISCUSSION

To our knowledge, DOCTOR is the only trial investigating alternative neoadjuvant treatment strategies (chemotherapy or chemoradiotherapy) for potentially curable EAC patients not showing an early response to initial CF. At study conception, doublet platinum-based chemotherapy (cisplatin or oxaliplatin) with a fluoropyrimidine was, and remains, a neoadjuvant therapy option for EAC based on OEO2,[28] OEO5,[29] and three national guidelines.[13–15] We previously reported a phase II randomised trial[8] comparing two cycles of presurgical CF with or without 35 Gy concurrent RT, finding no difference in survival. Hence, CF was chosen as the initial chemotherapy for DOCTOR with the addition of docetaxel for metabolic non-responders. This choice is supported by the results from FLOT4-AIO, which showed improved major histological response rates, PFS, and OS for FLOT compared with perioperative ECF/X for gastric and gastro-oesophageal junction cancer.[4] FLOT would now be considered a standard of care for EAC.

To date, four clinical trials have investigated early PET response-based therapy for EAC. In MUNICON I and II,[22,23] early responders received up to five cycles of preoperative chemotherapy, while the non-responders went directly to surgery or received RT *with the same chemotherapy.* Neither approach improved survival outcomes for non-responders. In CALGB 80803,[30] metabolic response was assessed after three cycles of oxaliplatin and 5-fluorouracil (FOLFOX-6) or four weekly cycles of carboplatin and paclitaxel, with crossover to the alternative regimen for non-responders and 50.4 Gy of concurrent RT for all patients. In the MEMORI study,[31] metabolic non-response to FOLFOX changed treatment to the CROSS regimen.

Early responders[21–23,31] consistently demonstrate survival outcomes superior to those achieved in biomarker-unselected patients,[1,4,5,10,26,28,29,32] and major histological response rates for EMR to chemotherapy are 33% to 44%. In contrast, only 7% of the early responders in DOCTOR showed a major histological response. Our shorter preoperative chemotherapy regimen may account for the reduced histological response and R0 rate observed.[22,23] However, the OS and PFS of the EMR group are similar to those in other PET response studies, with a low rate of LR that is similar to that achieved with chemoradiation regimens.[10,26]

Metabolic non-responders are a poor prognostic group. If non-responders continue on the same chemotherapy (Ott et al.[21]), or go directly to surgery (MUNICON I),[22] the major histological response rate is <5%, median PFS 10–14 months, and median OS 18–26 months. In DOCTOR, the addition of docetaxel to CF for metabolic non-responders resulted in an improved major histological response to 20%, meeting our primary end point. The change to continuous infusional 5-FU may have provided additional benefit.[33] In comparison, FLOT4-AIO reported a higher major histological response rate (36%) as well as better OS (median 50) for FLOT than did DCF for metabolic non-responders in our study (30 months).[3] This may represent the chemo-resistant nature of the metabolic non-responders, or our small study size. Indeed, higher

Table 3. Survival and recurrence

Characteristic	Value[a]	PET responders: CF (*N* = 45)	PET non-responders randomised: DCF (*N* = 31)	PET non-responders randomised: DCF + radiation (*N* = 35)	Others (*N* = 13)	All patients (*N* = 124)
PFS events	Yes	26 (58)	24 (77)	19 (54)	9 (69)	78 (63)
Event type	Death without documented progression	3 (12)	2 (8)			5 (6)
	Local relapse (follow-up)	3 (12)	7 (29)	2 (11)	1 (11)	13 (17)
	Distant relapse (follow-up)	18 (69)	10 (42)	14 (74)	6 (67)	48 (62)
	Both local and distant relapse (follow-up)	2 (8)	2 (8)	1 (5)		5 (6)
	Other relapse (follow-up)		1 (4)			1 (1)
	Progression of local disease (surgery)		1 (4)	1 (5)		2 (3)
	New metastatic disease (surgery)		1 (4)	1 (5)		2 (3)
	Tumour progression (end of study treatment)				2 (22)	2 (3)
Recurrence where known	Local relapse (follow-up)	3 (13)	7 (32)	2 (11)	1 (11)	13 (18)
	Distant relapse (follow-up)	18 (78)	10 (45)	14 (74)	6 (67)	48 (66)
	Both local and distant relapse (follow-up)	2 (9)	2 (9)	1 (5)		5 (7)
	Other relapse (follow-up)		1 (5)			1 (1)
	Progression of local disease (surgery)		1 (5)	1 (5)		2 (3)
	New metastatic disease (surgery)		1 (5)	1 (5)		2 (3)
	Tumour progression (end of study treatment)				2 (22)	2 (3)
Dead	Yes	23 (51)	21 (68)	19 (54)	9 (69)	72 (58)
Cause of death	Death from cancer	20 (87)	20 (95)	19 (100)	9 (100)	68 (94)
	Death from other cause	3 (13)	1 (5)			4 (6)
PFS at 36 months, [% (95% CI)]		47 (31—61)	29 (15—45)	46 (29—61)	37 (13—62)	41 (32—49)
OS at 60 months [% (95% CI)]		53 (37—67)	31 (16—48)	46 (29—61)	35 (11—60)	43 (34—52)
Median (95% CI) PFS (months)		27 (12—.)[b]	22 (14—27)	22 (14—.)[b]	13 (5—.)[b]	22 (15—36)
Median (95 % CI) OS (months)		61 (26—.)[b]	30 (17—55)	35 (20—.)[b]	31 (5—.)[b]	36 (25—61)
Median (95% CI) follow-up (months)		62 (59—62)	64 (49—64)	63 (45—64)	63 (15—63)	62 (60—64)

CF, cisplatin and 5-fluorouracil chemotherapy; CI, confidence interval; DCF, docetaxel, cisplatin, and 5-fluorouracil; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival.

[a] Values are *n* (%) unless otherwise indicated.

[b] Upper confidence limits could not be established.

locoregional failure rate (32%) for the metabolic non-responder patients who received DCF alone highlights the aggressive biological nature of EAC that does not show an EMR.

In DOCTOR, the addition of RT to DCF for metabolic non-responder patients resulted in a major histological response rate of 63%. The MEMORI and CALGB studies also demonstrate high response rates by changing chemotherapy with concurrent RT for metabolic non-responders. Significantly, the results from DOCTOR show similar 3-year PFS (47%) for EMR patients and metabolic non-responder (46%) patients randomised to DCFRT, with 5-year OS 53% and 46% for EMR and metabolic non-responders, respectively.[34] Hence, adding docetaxel, continuous 5-FU (rather than intermittent[33]) and RT may have closed the gap in survival outcomes between EMR and metabolic non-responder patients; a larger confirmatory study would be required.

DOCTOR allows focus on several aspects of neoadjuvant therapy. First, higher major histological response rates do not necessarily translate into better survival outcomes. Here, EMRs demonstrated lower histological RRs than did metabolic non-responders in arms A or B, but similar or superior PFS and superior OS. These findings were supported by a meta-analysis of 22 neoadjuvant EAC trials reporting that pathological complete response (pCR) rates did not correlate with OS.[11,35]

Second, should EMR patients receive more cycles of chemotherapy, continuous 5-FU or docetaxel? With FLOT now being considered a standard of care for EAC, starting with doublet chemotherapy may be less relevant, despite the favourable outcomes shown for the EMR in DOCTOR. Treatment options for early metabolic non-responders to FLOT require further study with greater numbers.

Third, the results from NeoRes,[10] MUNICON II,[23] and a randomised phase II study[8] all reported that higher histologic response rates did not result in better survival outcomes for neoadjuvant chemoradiotherapy over chemotherapy alone in biomarker-unselected patients. DOCTOR has demonstrated that the addition of docetaxel and RT to CF for metabolic non-responder patients resulted in LR rates and PFS comparable with those showing an EMR, albeit with significantly increased toxicity, although OS was still inferior.

Finally, is EMR a reliable biomarker? Our study design does not allow us to directly address this question since metabolic non-responders received additional alternative therapy, obscuring the prognostic value of EMR. Moreover, small sample size limits our ability to draw robust conclusions regarding survival outcomes. These questions could be addressed in a future randomised phase III trial aiming to assess the predictive value of an early PET scan in changing versus not changing subsequent neoadjuvant therapy.

In conclusion, DOCTOR has shown that biomarker-directed therapy for EAC, using EMR, is feasible, and that DCF, with or without RT, is an active regimen that can enhance primary histological responses. Moreover, those with an EMR to CF show very favourable survival and recurrence rates. The addition of docetaxel and RT to CF for metabolic non-responders results in similar PFS outcomes and appears better than the addition of docetaxel alone. However, further improvements in OS are needed. Future directions in adenocarcinoma treatment should consider EMR, other biomarkers, incorporation of immunotherapies, and other novel treatments to tailor therapy to patients most likely to benefit from this approach.

ACKNOWLEDGEMENTS

DOCTOR was sponsored by the Australasian Gastro-Intestinal Trials Group and coordinated by the National Health & Medical Research Council Clinical Trials Centre, University of Sydney. We thank Sanofi Aventis Australia Pty Ltd for providing the docetaxel.

DOCTOR INVESTIGATORS

Trial Management Committee: A Barbour (Chair), J Simes, E Walpole, T Mai, D Watson, C Karapetis, V Gebski, L Barnes, M Oostendorp, K Wilson.

Clinical Trials Centre: J Simes, V Gebski, L Barnes, M Oostendorp, K Wilson.

Study sites: The following study sites participated in the DOCTOR study and randomised at least one patient; principal investigator (PI), medical oncologist (MO), radiation oncologist (RO), surgeon (SU), nuclear medicine (NM), and site coordinator (SC):

- Calvary Mater Newcastle (14), New South Wales: Prof. Stephen Ackland (PI), Prof. Jarad Martin (RO), Dr Mahesh Kumar (RO), Dr Swetha Sridaran (RO), Dr Ann Capp (RO), Dr Girish Mallesara (MO), Dr James Lynam (MO), Dr Andre van der Westhuizen (MO), Dr Fiona Day (MO), Dr Vanessa Wills (SU), Megan Livingston (SC), Kim Adler (SC)
- Nepean Hospital (1), New South Wales: Dr Jenny Shannon (PI), Dr Mark Richardson (SU), Dr Han Liem (SU), Dr Tim Wang (RO), Dr Amanda Stevanovic (MO), Junie McCourt (SC), Jeremy Jones (SC)
- Sydney Adventist Hospital (1), New South Wales: A/Prof. Gavin Marx (PI), Dr Joseph Rutovitz (MO), A/Prof. Gregory Falk (SU), Meenal Gupta (SC), Nina Singh (SC)
- Royal Brisbane and Women's Hospital (9), Queensland: Dr Matthew Burge (PI), Dr David Wyld (MO), Dr Melissa Eastgate (MO), Dr Alison Hadley (MO), Dr Graham Dickie (RO), Dr Robert Finch (SU), Andrea McKenzie (SC)
- Princess Alexandra Hospital (34), Queensland: Prof Andrew Barbour (PI), Prof. Euan Walpole (MO), A/Prof. Victoria Atkinson (MO), Dr Warren Joubert (MO), Dr Damian Thomson (MO), Dr Liz McCaffrey (MO), Dr Margaret McGrath (MO), Prof. Bryan Burmeister (RO), Dr Jennifer Harvey (RO), Dr Gang Tao Mai (RO), Dr David Pryor (RO), Prof. Mark Smithers (SU), Professor David Gotley (SU), Dr Iain Thomson (SU), Dr Stanley Ngai (NM), Janine Thomas (SC), Jennifer Addison (SC), Ben Shea (SC)
- Townsville Hospital (1), Queensland: Dr Suresh Varma (PI), Dr Donald Cameron (SU), Dr Alex Tran (RO), Dr

Abhishek Joshi (MO), Judith Page (SC), Elizabeth Heyer (SC)

- Flinders Medical Centre (4), South Australia: Prof Chris Karapetis (PI), Dr Amitesh Roy(MO), Dr Tim Bright (SU), Prof. David Wattchow (SU), Alison Richards (SC), Monique Swan (SC), Alex Scott-Hoy (SC), Kelly Mead (SC)
- Royal Hobart Hospital (2), Tasmania: Dr Louise Nott (PI), Dr Allison Black (MO), Dr David Boadle (MO), Dr Ian Byard (MO), Dr John Ward (RO), Dr Eric Kim (RO), Dr Robert Bohmer (SU), Elizabeth Campbell-Taylor (SC), Elizabeth Hammer (SC)

FUNDING

This study was funded by the National Health & Medical Research Council (Project Grant number 1011782). Sanofi Aventis Australia Pty Ltd (no grant number) provided docetaxel.

DISCLOSURE

LMN has served on the Advisory Board of Roche, MSD. All other authors have declared no conflicts of interest.

REFERENCES

1. Stahl M, Walz MK, Stuschke M, et al. Phase III comparison of preoperative chemotherapy compared with chemoradiotherapy in patients with locally advanced adenocarcinoma of the esophagogastric junction. *J Clin Oncol*. 2009;27(6):851–856.
2. Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med*. 1996;335(7):462–467.
3. Al-Batran SE, Hofheinz RD, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): Results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. *Lancet Oncol*. 2016;17(12):1697–1708.
4. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): A randomised, phase 2/3 trial. *Lancet*. 2019;393(10184):1948–1957.
5. Tepper J, Krasna MJ, Niedzwiecki D, et al. Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781. *J Clin Oncol*. 2008;26(7):1086–1092.
6. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med*. 2012;366(22):2074–2084.
7. Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: A randomised controlled phase III trial. *Lancet Oncol*. 2005;6(9):659–668.
8. Burmeister BH, Thomas JM, Burmeister EA, et al. Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial. *Eur J Cancer*. 2011;47(3):354–360.
9. Gebski V, Burmeister B, Smithers BM, et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: A meta-analysis. *Lancet Oncol*. 2007;8(3):226–234.
10. Klevebro F, Alexandersson von Dobeln G, et al. A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction. *Ann Oncol*. 2016;27(4):660–667.
11. Sjoquist KM, Burmeister BH, Smithers BM, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. *Lancet Oncol*. 2011;12(7):681–692.
12. Urba SG, Orringer MB, Turrisi A, et al. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. *J Clin Oncol*. 2001;19(2):305–313.
13. National Institute for Health and Care Excellence. Oesophago-gastric cancer: Assessment and management in adults 2018. Available at https://www.nice.org.uk/guidance/ng83. Accessed November 22, 2019.
14. Lordick F, Mariette C, Haustermans K, et al. Oesophageal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27(suppl 5):v50–v57.
15. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: esophageal and esophagogastric junction cancers; 2017. Available at http://www.nccn.org/. Accessed November 22, 2019.
16. Becker K, Mueller JD, Schulmacher C, et al. Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. *Cancer*. 2003;98(7):1521–1530.
17. Davarzani N, Hutchins GGA, West NP, et al. Prognostic value of pathological lymph node status and primary tumour regression grading following neoadjuvant chemotherapy - Results from the MRC OE02 oesophageal cancer trial. *Histopathology*. 2018;72(7):1180–1188.
18. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer*. 1994;73(11):2680–2686.
19. Smyth EC, Fassan M, Cunningham D, et al. Effect of pathologic tumor response and nodal status on survival in the Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial. *J Clin Oncol*. 2016;34(23):2721–2727.
20. Swisher SG, Hofstetter W, Wu TT, et al. Proposed revision of the esophageal cancer staging system to accommodate pathologic response (pP) following preoperative chemoradiation (CRT). *Ann Surg*. 2005;241(5):810–817. discussion 7–20.
21. Ott K, Weber WA, Lordick F, Becker K, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. *J Clin Oncol*. 2006;24(29):4692–4698.
22. Lordick F, Ott K, Krause BJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: The MUNICON phase II trial. *Lancet Oncol*. 2007;8(9):797–805.
23. zum Buschenfelde CM, Herrmann K, Schuster T, et al. (18)F-FDG PET-guided salvage neoadjuvant radiochemotherapy of adenocarcinoma of the esophagogastric junction: The MUNICON II trial. *J Nucl Med*. 2011;52(8):1189–1196.
24. Amin MB, Edge S, Greene F, et al., eds. *AJCC Cancer Staging Manual*. New York: Springer International; 2017.
25. Barbour AP, Jones M, Gonen M, et al. Refining esophageal cancer staging after neoadjuvant therapy: importance of treatment response. *Ann Surg Oncol*. 2008;15(10):2894–2902.
26. Oppedijk V, van der Gaast A, van Lanschot JJ, et al. Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials. *J Clin Oncol*. 2014;32(5):385–391.
27. Gebski V, Gares V, Gibbs E, et al. Data maturity and follow-up in time-to-event analyses. *Int J Epidemiol*. 2018;47(3):850–859.
28. Allum WH, Stenning SP, Bancewicz J, et al. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol*. 2009;27(30):5062–5067.
29. Alderson D, Cunningham D, Nankivell M, et al. Neoadjuvant cisplatin and fluorouracil versus epirubicin, cisplatin, and capecitabine followed by resection in patients with oesophageal adenocarcinoma (UK MRC OE05): An open-label, randomised phase 3 trial. *Lancet Oncol*. 2017;18(9):1249–1260.

30. Goodman KA, Niedzwiecki D, Hall N, et al. Initial results of CALGB 80803 (Alliance): a randomized phase II trial of PET scan-directed combined modality therapy for esophageal cancer. *J Clin Oncol*. 2017;35(4 suppl):1.
31. Lorenzen S, Quante M, Rauscher I, et al. PET-directed combined modality therapy for gastroesophageal junction cancer: First results of the prospective MEMORI trial. *J Clin Oncol*. 2019;37(15_suppl):4018.
32. Kelsen DP, Ginsberg R, Pajak TF, et al. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med*. 1998;339(27):1979—1984.
33. Grothey A, Sobrero AF, Shields AF, et al. Duration of adjuvant chemotherapy for stage III colon cancer. *N Engl J Med*. 2018;378(13):1177—1188.
34. Barbour A, Walpole ET, Mai GT, et al. An AGITG trial —A randomised phase II study of pre-operative cisplatin, fluorouracil and DOCetaxel +/-radioTherapy based on poOR early response to cisplatin and fluorouracil for resectable esophageal adenocarcinoma. *Ann Oncol*. 2016;27(suppl 6):6100.
35. Petrelli F, Tomasello G, Barni S. Surrogate end-points for overall survival in 22 neoadjuvant trials of gastro-oesophageal cancers. *Eur J Cancer*. 2017;76:8—16.

original article

Eur Surg (2020) 52:22–28
https://doi.org/10.1007/s10353-019-00620-4

european surgery
ACA Acta Chirurgica Austriaca

Regional pain management for oesophagectomy: Cohort study suggests a viable alternative to a thoracic epidural to enhance recovery after surgery

Rakesh Rai · Anthony Notaras · Philip Corke · Gregory L. Falk

Received: 23 October 2019 / Accepted: 12 November 2019 / Published online: 8 January 2020

Summary
Background Ivor Lewis oesophagectomy (ILO) is associated with significant acute postsurgical pain and persistent chronic pain. The purpose of this study was to compare the Concord technique, which involves a combination of a surgeon-inserted paravertebral catheter, a single injection of intrathecal morphine and surgeon-inserted bilateral preperitoneal catheters, with the other available analgesic techniques.
Methods The study was designed as a retrospective cohort study and performed at the Concord Repatriation General Hospital, a tertiary teaching hospital affiliated with Sydney University. The participants comprised 60 consecutive patients in whom ILO was undertaken from January 1, 2011 to December 31, 2017, who were retrospectively analysed according to analgesic technique. The maximum, minimum and average pain numerical rating scale (NRS) scores were prospectively recorded daily for 3 days, opioid use for 3 days, and hospital length of stay, intensive care unit (ICU) length of stay, 30-day mortality and postoperative complications were also recorded.
Results The Concord regional anaesthetic technique group had an average NRS pain scores which appeared favourable for day 0 (0.90 vs. 1.42), but no statistical differences were found between either group on day 1 (1.34 vs. 1.54), day 2 (0.94 vs. 1.13) or day 3 (0.94 vs. 1.00). The 30-day mortality, length of stay in hospital and ICU, and postoperative complications were comparable.
Conclusion The Concord regional technique for ILO analgesia appears to provide a simple alternative to other forms of analgesia, with similar analgesic efficacy and with no differences in postoperative complications. This may provide a pathway to enhanced recovery and is suitable to be evaluated in a Randomised control trial (RCT) of techniques.

Keywords Intrathecal morphine · Oesophagectomy analgesia · Concord technique · Paravertebral catheter

Main novel aspects

- There appears to be equipoise between thoracic epidural and regional analgesia for oesophagectomy
- Regional pain management is likely beneficial to ERAS protocols
- It appears justified to perform an RCT of regional and TCA management in oesophagectomy

Introduction

The Ivor Lewis oesophagectomy (ILO) involves a midline laparotomy and a right-sided thoracotomy, and has been associated with significant acute postoperative pain and persistent prolonged postsurgical pain in 30–50% of patients [1]. The management of this acute post-oesophagectomy pain presents a number of challenges, due to its effect on respiratory function,

Dr. R. Rai, MBBS FCICM FANZCA (✉) · A. Notaras, MBBS
Department of Anaesthesia, Concord Repatriation General Hospital, Sydney, NSW, Australia
brakeshrai@hotmail.com

P. Corke, MBBS FANZCA FFPMANZCA
Acute Pain Service, Concord Repatriation General Hospital, Sydney, NSW, Australia

G. L. Falk, MBBS FRACS FACS
Department of Upper Gastro-Intestinal Surgery, Concord Repatriation General Hospital, Sydney, NSW, Australia

Dr. R. Rai, MBBS FCICM FANZCA
Suite 29, 12 Tryon Road, 2070 Lindfield NSW, Australia

increased cardiac work and the potential for chronic pain. Effective perioperative analgesia is vital in reducing morbidity (60%) and allowing for early mobilization of the patient [2].

Thoracic epidural analgesia (TEA) is currently the mainstay technique in many centres. It has been well established that TEA in oesophagectomy reduces pain both at rest and during movement, has fewer opioid-induced side effects and a lower rate of chronic post-surgical pain compared with intravenous morphine analgesia [3–5]. There is growing evidence supporting the use of paravertebral blocks (PVB) for early thoracotomy pain, with recent studies demonstrating similar efficacy between PVB and TEA but with fewer complications [6–8].

An analgesia technique that can avoid technical difficulties, labour intensity and serious complications (nerve injury, spinal cord damage, spinal haematoma, abscess) which are associated with a TEA is warranted.

Phillips et al. [9] reported on a technique combining a PVB with bilateral preperitoneal catheters and patient-controlled epidural pethidine as rescue analgesia. They compared this technique to TEA and demonstrated comparable pain scores but reduced use of inotropes, intensive care stay, reintubation and early mobilization [9].

Similarly, we utilised a perioperative analgesic technique ("Concord technique", CT) for patients undergoing ILO that incorporates a combination of surgically placed paravertebral catheter (PVB), a single injection of intrathecal morphine and two preperitoneal ropivacaine continuous infusions. Rescue analgesia was through parenteral opioid patient-controlled analgesia (PCA).

We hypothesized that there would be no superiority in postoperative outcomes for patients who received the Concord technique (CT) in comparison to those patients that received other established post-oesophagectomy analgesic regimes.

Materials and methods

Patient records of those having ILO between January 2011 and December 2017 at a single-site public hospital by a single surgeon were extracted.

The perioperative course of patients undergoing oesophagectomy was subject to the surgeon's long-standing oesophagectomy Enhanced Recovery After Surgery (ERAS) protocol.

Patients

Patients having ILO with a midline laparotomy and right-sided thoracotomy for oesophageal cancer at Concord Hospital from January 1, 2011, to December 31, 2017 were eligible. Patients were excluded if surgery was performed in a way other than open laparotomy and right-sided thoracotomy or incomplete data were available from the medical record system.

Anaesthesia and analgesia

Induction of anaesthesia was performed with propofol, fentanyl and rocuronium, maintenance with sevoflurane or desflurane and incremental doses of fentanyl. All patients had one lung ventilation with a double-lumen tube during thoracotomy.

Patients in the Concord technique group received the following analgesia:

1. Intrathecal morphine 200 micrograms at the start of the case under strict asepsis using a 25 G pencil point needle at the L 3–5 space.
2. Two preperitoneal 20 G multi-holed catheters inserted by the surgeon approximately 3 cm from the lower end of the midline incision. The catheter was then connected to an elastomeric balloon pump (ON-Q® PainBuster®, B. Braun Melsungen AG, Melsungen, Deutschland) pre-filled with 0.2% ropivacaine at 5 ml/h to last up to 110 h.
3. Right, paravertebral 20 G multi-holed catheter inserted by the surgeon from two intercostal spaces below the thoracotomy and about 5 cm from midline posteriorly. The catheter was then connected to an elastomeric balloon pump (On-Q device) pre-filled with 0.2% ropivacaine at 5 ml/h to last up to 110 h.
4. Intravenous fentanyl or morphine titrated to effect intraoperatively.
5. Intravenous fentanyl or morphine PCA postoperatively.
6. Intravenous regular paracetamol postoperatively

The patients were retrospectively allocated into patients that received the Concord technique analgesia regime in one group (CT) and in the other group (NCT) those that did not.

All patients had a mediastinal drain, two intercostal catheters placed in the right pleural cavity, a urinary catheter and a nasogastric tube. All patients underwent extubation unless the attending anaesthetist deemed that ongoing mechanical ventilation was warranted. All patients were managed in the ICU.

Hourly vital observations and pain scores using the numerical rating scale (NRS) during wakefulness and the Critical Care Pain Observation Tool (CPOT) while the patient was asleep were performed routinely. The integrated pain service led by an anaesthetist/pain specialist reviewed the patient daily.

Data collection

Data were obtained from medical records including the anaesthetic record, medication prescription charts and ICU observation charts. Existing comorbidities were tabulated.

The hourly pain NRS and CPOT ratings were averaged for each day until day 3 post-procedure (day 0 was deemed the day of the operation). Maximal and minimal daily pain ratings were all recorded. The

Table 1 Demographics

	All patients ($n=59$)	Non-CT technique ($n=27$)	Concord technique ($n=32$)
Age (years)			
Median	65	66	64.5
IQR	[57–72]	[56–74]	[57.75–69.75]
Gender (n, %)			
Female	7 (11.9%)	4 (14.8%)	3 (9.4%)
Male	52 (88.1%)	23 (85.2%)	27 (90.6%)
Preoperative weight (kg)			
Median	83	85	81.5
IQR	[66–92]	[66–93]	[66.25–91.50]
Comorbidities (n, %)			
CCF	3 (5.1%)	1 (3.7%)	2 (6.3%)
IHD	12 (20.3%)	6(22.2%)	6 (18.8%)
T2DM	7 (11.9%)	3 (11.1%)	4 (12.5%)
COPD	11 (18.6%)	5 (18.5%)	6 (18.8%)
OSA	2 (3.4%)	0	2 (6.3%)
Chronic Pain	2 (3.4%)	0	2 (6.3%)

IQR Interquartile range, *CCF* Congestive cardiac failure, *IHD* Ischaemic heart disease, *T2DM* Type 2 diabetes mellitus, *COPD* Chronic obstructive pulmonary disease, *OSA* Obstructive sleep apnea

usage of Patient controlled analgesia (PCA) and any rescue analgesia was collated for 72 h postoperatively. Patient-controlled analgesia (PCA) was standardised to fentanyl/equivalent doses (morphine). The PCA usage information was obtained from the ICU chart. This provided an hourly cumulative total of IV analgesia used.

Postoperative data included ICU length of stay, hospital length of stay, in-hospital mortality, extubation at emergence, postoperative reintubation, vasopressors 24 h from arrival in the ICU and fluids administered for 24 h from arrival in the ICU. Postoperative complications were recorded (Table 5). Respiratory depression was defined as a respiratory rate of fewer than 8 breaths/min within 72 h from ICU admission or the continuation of mechanical ventilation after day 1 (failed planned extubation).

Statistical analysis

Incidences were reported as median values with interquartile ranges where appropriate. Groups were compared using Pearson chi-squared analysis for categorical variables and independent sample t-test for continuous data. Level of significance was set at $P<0.05$ and data were analysed using SPSS for Windows (version 21 IBM Corp, Armonk, NY, USA).

Results

During the 7-year period, 60 patients underwent an Ivor Lewis oesophagectomy. One patient was excluded for inadequate data. The CT was performed in 32 patients and NCT in 27 patients (Table 1).

Patients in the NCT group received a varied range of intraoperative analgesia (Table 2).

Postoperatively (Table 3), three of the patients were continued on an epidural fentanyl/ropivacaine infusion, five patients received pethidine epidural analgesia postoperatively. The remaining patients in the NCT group received components of the CT but not in its entirety.

Both groups were similar in terms of intraoperative intravenous opioid consumption (Table 3: 500 mcg vs. 450 mcg), and neither group had significantly different fentanyl consumption in 72 h (2500 mcg vs. 3160 mcg; $p=0.417$). The NCT group required further rescue analgesia (7 vs. 1; $p=0.011$), with the addition of ketamine and/or an increase in PCA bolus dose within the 72 h postoperative period ($p=0.51$ and $p=0.53$, respectively).

The regional analgesia group (CT) may have been advantaged on day 0 (Table 4: $p=0.058$). No difference could be detected over the 72-hour period. Postoperative complications are detailed in Table 5 and were comparable.

Table 2 Intraoperative analgesia

	All patients ($n=59$)	Non-CT technique ($n=27$)	Concord technique ($n=32$)	*p*-value
Intrathecal morphine	42 (71.2%)	10 (37%)	32 (100%)	–
Epidural morphine	1 (1.7%)	1 (3.7%)	0	0.186
Intrathecal bupivacaine	4 (6.8%)	2 (7.4%)	2 (6.3%)	0.272
Epidural bupivacaine	1 (1.7%)	1 (3.7%)	0	0.005
Epidural fentanyl	6 (10.2%)	6 (22.2%)	0	0.053
Epidural ropivacaine	4 (6.8%)	4 (14.8%)	0	0.024
Remifentanil	3 (6.8%)	2 (7.4%)	1 (3.1%)	0.456
Tramadol	16 (27.1%)	8 (29.6%)	8 (25%)	0.690
Ketamine	11 (18.6%)	7 (25.9%)	4 (12.5%)	0.187
Intraoperative IV Fentanyl (mcg)				
Median	500	500	450	0.417
IQR	[350–680]	[300–700]	[350–600]	–

IQR Interquartile range, *CT* Concord technique, *IV* intravenous

Table 3 Postoperative analgesia

	All patients ($n=59$)	Non-CT technique ($n=27$)	Concord technique ($n=32$)	p-value
Paravertebral catheter	53 (89.8)	21 (77.8%)	32 (100%)	0.005
Preperitoneal catheters				
No preperitoneal catheters	12 (20.3%)	12 (44.4%)	0	
One preperitoneal catheter	4 (6.8%)	4 (14.8%)	0	–
Two preperitoneal catheters	43 (72.9%)	11 (40.7%)	32 (100%)	–
PCEA pethidine	5 (8.5%)	5 (18.5%)	0	0.011
Epidural ropivacaine	3 (5.1%)	3 (11.1%)	0	0.053
Epidural fentanyl	4 (6.8%)	4 (14.8%)	0	0.024
Postop ketamine infusion (predetermined)	6 (10.2%)	4 (14.8%)	2 (6.3%)	0.278
PCA				
PCA fentanyl	47 (79.7%)	18 (66.7%)	29 (90.6%)	–
PCA morphine	9 (15.3%)	6 (22.2%)	3 (9.4%)	–
No PCA	3 (5.1%)	3 (11.1%)	0	–
PCA fentanyl equivalent (mcg) [72 h postop]				
Median	2970	2500	3160	0.417
IQR	[2040–3900]	[895–4120]	[2134–3875]	–
Postop rescue analgesia (72 h postop)				0.011
Ketamine	6 (10.2%)	5 (18.5%)	1 (3.1%)	0.051
Increase PCA bolus	3 (5.1%)	3 (11.1%)	0	0.053
Rescue epidural	1 (1.7%)	1 (3.7%)	0	0.272

CT Concord Technique; *PCEA* Patient controlled epidural analgesia; *PCA* Patient controlled analgesia; *IQR* Interquartile range

Table 4 Postoperative pain scores

Pain scores (median) [IQR]	All patients ($n=59$)	Non-CT technique ($n=27$)	Concord technique ($n=32$)	p-value
Day 0				
NRS min	0 [0–0]	0 [0–0]	0 [0–0]	–
NRS max	4 [2.00–7.00]	5 [2.00–8.00]	4 [1.25–6.75]	0.464
NRS avg	1 [0.20–2.30]	1.42 [0.32–3.3]	0.90 [0.12–1.47]	0.058
Day 1				
NRS min	0 [0–0]	0 [0–0]	0 [0–0]	–
NRS max	5 [3.00–7.00]	5 [2.00–7.00]	5.5 [4.00–7.75]	0.235
NRS avg	1.41 [0.79–2.88]	1.54 [0.79–2.92]	1.35 [0.79–2.75]	0.351
Day 2				
NRS min	0 [0–0]	0 [0–0]	0 [0–0]	–
NRS max	4 [2.00–6.00]	4 [2.00–6.00]	4 [3.00–6.00]	0.997
NRS avg	1.04 [0.40–2.20]	1.13 [0.58–2.20]	0.94 [0.38–2.29]	0.779
Day 3				
NRS min	0 [0–0]	0 [0–0]	0 [0–0]	–
NRS max	4 [3.00–6.00]	4 [2.00–7.00]	5 [3.00–6.00]	0.487
NRS avg	0.39 [1.00–1.50]	1 [0.29–1.41]	0.94 [0.25–1.50]	0.871

NRS Numerical rating score, *min* minimum, *avg* average, *max* maximum

Mortality was from cardiovascular accident, sepsis and respiratory failure.

There was no difference in the causes or frequencies of respiratory depression in either group. Patients in the regional CT group were more likely to be extubated at the end of the case (Table 5: 77.8% vs. 96.9%, $p=0.024$).

Discussion

The CT, in comparison to other analgesic techniques for oesophagectomy, provided equivalent analgesic efficacy and postoperative parenteral opioid use to traditional analgesic techniques. A reduction in the need for rescue analgesia was also apparent.

Table 5 Postoperative complications

Type of analgesia	All patients ($n=59$)	Non-CT technique ($n=27$)	Concord technique ($n=32$)	*p*-value
Postoperative patient outcomes (median) [IQR]				
ICU days				0.286
Median	*5*	*5*	*5.5*	
IQR	*[4–6]*	*[4–6]*	*[4–6]*	
Hospital days				0.700
Median	*16*	*15*	*16.5*	
IQR	*[13–17]*	*[14–29]*	*[12.25–24.75]*	
30-day mortality	3 (5.1%)	1 (3.7%)	2 (6.3%)	0.657
Extubated at end of procedure	52(88.1%)	21 (77.8%)	31 (96.9%)	*0.024*
Postop reintubation	2 (3.4%)	1 (3.7%)	1 (3.1%)	0.903
Pruritus	1 (1.7%)	0	1 (3.1%)	0.354
Respiratory depression	6 (10.2%)	4 (14.8%)	2 (6.3%)	0.278
Hallucinations	3 (5.1%)	1 (3.7%)	2 (6.3%)	0.657
Confusion	1 [1.7%]	0	1 (3.1%)	0.354
Anastomotic leak	8(13.6%)	4 (14.8%)	4 (12.5%)	0.826
Chyle leak	3 (5.1%)	0	3 (9.4%)	0.102
Arrhythmia	15 (25.4%)	6 (22.2%)	9 (28.1%)	0.604
VTE	5 (8.5%)	1 (3.7%)	4 (12.5%)	0.227
Catheter displacement or catheter infection	3 [5.1%]	1 (3.7%)	2 (6.3%)	0.657
Postop naloxone [72 h]	2 (3.4%)	1 (3.7%)	1 (3.1%)	0.903
Postop inotropes [24 h]	14 (23.7%)	7 (25.9%)	7 (21.9%)	0.716
Postop crystalloids (L) [24 h]				0.426
Median	*2.22*	*2.26*	*2.2*	
IQR	*[1.62–2.90]*	*[1.62–3.50]*	*[1.60–2.80]*	
Postop colloids (L) [24 h]				–
Median	*0.2*	*0.2*	*0.2*	
IQR	*[0.2–0.2]*	*[0.2–0.2]*	*[0.2–0.2]*	

ICU Intensive care unit, *VTE* Venous thromboembolism, *IQR* Inter quartile range

PVB for post-thoracotomy analgesia has been shown to provide better analgesia, fewer side effects and better preservation of lung function in comparison with TEA [27].

Intrathecal morphine was included in the CT technique, given the purported superior postoperative analgesia for major abdominal and cardiothoracic procedures compared with other opioid analgesic techniques [22, 23].

The addition of two pre-peritoneal catheters of 0.2% ropivacaine at 5 ml/h each provides effective analgesia for post-laparotomy pain [11]. It provides a significant benefit over systemic analgesia both on pain at rest and mobilisation for major abdominal surgery [11]. The ease of placement of preperitoneal catheters mitigates the potential insertion complications associated with TEA. The present study does not have data on mobilisation, but the experience appeared favourable in allowing early ERAS pursuit, especially in the prolonged ICU stays experienced with TEA hypotension and requirement to remain bed bound.

Dose

The combined total infusion rate of 0.2% ropivacaine at 15 ml/h via the two preperitoneal and one paravertebral catheter is equivalent to that reported by Phillips et al. [9]. Suggested paravertebral continuous infusion rates have been reported at 5–10 ml/h of 0.2% ropivacaine [15]. Similarly, preperitoneal infusions of 0.2% ropivacaine at 10 ml/h provide analgesic benefits over systemic analgesia alone [11, 28]. There were no cases of local anaesthetic toxicity in our study or the Phillips' study.

Complications

The introduction of ERAS protocols [18], high-volume centres, multi-speciality team approaches and advances in surgical technique have improved morbidity and mortality rates of oesophagectomy [17, 29], which can still remain high with morbidity of 30–50% and mortality of 2–10% [19, 20].

There was no difference in mortality rates between either group, with an overall in-hospital mortality of

5.1%, which is comparable with many large centres using TEA [21, 28].

Several studies report a decline in morbidity and mortality with the introduction of TEA when compared to traditional parenteral analgesic techniques [12]. TEA is also considered as an independent factor for prevention of pneumonia, pulmonary complications and a key determinant reducing mortality rates [26].

Studies that have compared PVB to TEA for post-thoracotomy pain show no difference in 30-day mortality, hospital stay or major complications [6]. PVB also lessens rates of urinary retention, nausea and vomiting, hypotension, pulmonary complications and block failure rates [7, 16, 24]. Specific to the use of PVB in oesophagectomy surgery, Phillips et al. [9] reported lower rates of inotrope use, shorter intensive care stay, and more rapid mobilisation.

This study, however, found an improvement in rates of immediate postoperative extubation but no difference in other major outcomes including respiratory complications, arrhythmias [10] and VTE.

The rates of postoperative cardiac arrhythmias were similar between groups and comparable to those previously reported (10–40%) [3, 9, 26].

Practically, TEA poses difficulties not limited to catheter displacement and epidural failure. Cense et al. [13] found an epidural failure rate of 32% and that 43% of epidural catheters were removed against postoperative protocols [12]. Reasons for epidural failure include pain, bloody catheter, dysfunction, catheter dislocation and hypotension. The regional technique obviates these issues [14].

Limitations

The retrospective nature of our study presents various limitations. There was marked heterogeneity of analgesic techniques in the NCT group, which may limit the application of differences between each group. Notwithstanding, the surgical team was consistent, and each patients postoperative management was standardised to the oesophagectomy ERAS protocol. As a result, within these limitations, associations can be drawn between CT, NCT and previously reported outcomes of traditional techniques. Further validation needs a large RCT to compare our technique with TEA in a high volume oesophagectomy centre.

Conclusion

The regional CT for postsurgical analgesia after ILO appears to provide an equivalent alternative to other forms of analgesia with similar analgesic efficacy and no differences in postoperative complications. This alternative may circumvent the other practical challenges of TEA not limited to catheter displacement and epidural failure, and the study provides pilot data for an RCT in high-volume centres.

Compliance with ethical guidelines

Conflict of interest R. Rai, A. Notaras, P. Corke and G.L. Falk declare that they have no competing interests.

Ethical standards Ethics approval for the study was obtained from the Human Research Ethics and Governance Committees at Concord Hospital, Sydney LNR/17/CRGH/134. The requirement for individual informed consent was waived.

References

1. De Cosmo G, Aceto P, Gualtieri E, Congedo E. Analgesia in thoracic surgery: review. Minerva Anestesiol. 2009;75(6):393–400.
2. Atkins BZ, Shah AS, Hutcheson KA, et al. Reducing hospital morbidity and mortality following esophagectomy. Ann Thorac Surg. 2004;78(4):1170–6.
3. Rudin A, Flisberg P, Johansson J, Walther B, Lindberg CJF. Thoracic epidural analgesia or intravenous morphine analgesia after thoracoabdominal esophagectomy: A prospective follow-up of 201 patients. J Cardiothorac Vasc Anesth. 2005;19(3):350–7.
4. Fares KM, Mohamed SA, Hamza HM. Effect of thoracic epidural analgesia on pro-inflammatory cytokines in patients subjected to protective lung ventilation during Ivor Lewis esophagectomy. Pain Physician. 2014;17(4):305–15.
5. Andreae MH, Andreae DA. Local anaesthetics and regional anaesthesia for preventing chronic pain after surgery. Cochrane Database Syst Rev. 2012; https://doi.org/10.1002/14651858.CD007105.pub2.
6. Yeung JHY, Gates S, Naidu BV, Wilson MJA, Gao SF. Paravertebral block versus thoracic epidural for patients undergoing thoracotomy. Cochrane Database Syst Rev. 2016; https://doi.org/10.1002/14651858.CD009121.pub2.
7. Davies RG, Myles PS, Graham JM. A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy—a systematic review and meta-analysis of randomized trials. Br J Anaesthesiol. 2006;96(4):418.
8. Joshi GP, Bonnet F, Shah R. A systematic review of randomized trials evaluating regional techniques for post thoracotomy analgesia. Anaesth Analg. 2008;107(3):1026–40.
9. Phillips S, Dedic-Hagan J, Baxter D, Van der Wall H, Falk G. A novel technique of paravertebral thoracic and preperitoneal analgesia enhances early recovery after oesophagectomy. World J Surg. 2018;42(6):1787–91.
10. Ahn HJ, Sim WS, Shim YM, Kim JA. Thoracic epidural anesthesia does not improve the incidence of arrhythmias after transthoracic esophagectomy. Eur J Cardiothorac Surg. 2005;28(1):19–21.
11. Beaussier M, El'Ayoubi H, Schiffer E, et al. Continuous preperitoneal infusion of ropivacaine provides effective analgesia and accelerates recovery after colorectal surgery: a randomized, double-blind, placebo-controlled study. Anesthesiology. 2007;107(3):461–8.
12. Birkmeyer JD, Stukel TA, Siewers AE, et al. Surgeon volume and operative mortality in the United States. N Engl J Med. 2003;349:2117–27.
13. Cense HA, Lagarde SM, de Jong K. Association of no epidural analgesia with postoperative morbidity and mortality after transthoracic esophageal cancer resection. J Am Coll Surg. 2006;202:395–400.
14. Cook E, Downs C. Analgesia after thoracotomy—the role of extrapleura paravertebral catheter. Aust Anaesth. 2005;103–16.

15. Chely JE, Ghisi D, Fanellii A. Continuous peripheral nerve blocks in acute pain management. Br J Anaesth. 2010;105:1.
16. Dango S, Harris S, Offner K, Hennings E, Preibe HJ, Buerkle H, et al. Combined paravertebral and intrathecal vs thoracic epidural analgesia for post-thoracotomy pain relief. Br J Anaesth. 2013;110(3):443–9.
17. Ding X, Jin S, Niu X, Ren H, Fu S, Li Q. A comparison of the analgesia efficacy and side effects of paravertebral compared with epidural blockade for thoracotomy: an updated meta-analysis. PLoS One. 2014;9(5):e96233. https://doi.org/10.1371/journal.pone.0096233.
18. Ford SJ, Adams D, Dudnikov S, Peyser P, Rahamim J, Whealey TJ, et al. The implementation and effectiveness of an enhanced recovery programme after oesophagogastrectomy: a prospective cohort study. Int J Surg. 2014;12(4):320–4.
19. Gotoda Y, Kambara N, Sakai T, Kishi Y, Kodama K. The morbidity, time course and predictive factors for persistent post-thoracotomy pain. Eur J Pain. 2001;5:89–96.
20. Muller JM, Erasmi H, Stelzner M, et al. Surgical therapy of oesophagealcarcinoma. Br J Surg. 1990;77:845–57.
21. Mariette C, Piessen G, Triboulet JP. Therapeutic strategies in oesophageal carcinoma: role of surgery and other modalities. Lancet Oncol. 2007;8:545–53.
22. Richardson J, Sabanathan S, Shah R. Post-thoracotomy spirometric lung function: the effect of analgesia. A review. J Cardiovasc Surg. 1999;40:445–56.
23. Meylan N, Elia N, Lysakowski C, Tramer MR. Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. Br J Anaesth. 2009;102(2):156–67.
24. Pennefater H. Anaesthesia for Oesophagectomy. Thorac Anaesth. 2007;20:15–20.
25. Richardson J, Sabanathan S, Jones J, et al. A prospective, randomized comparison of preoperative and continuous balanced epidural or paravertebral bupivacaine on post-thoracotomy pain, pulmonary function and stress responses. Brit J Anaesth. 1999;83:387–92.
26. Rosenberg J, Kehlet H. Does effective postoperative pain management influence surgical morbidity? Eur Surg Res. 1999;31:133–7.
27. Scarfe AJ, Schuhmann-Hingel S, Duncan JK, Ma N, Atukorale YN, Cameron AL. Continuous paravertebral block for post-cardiothoracic surgery analgesia: a systematic review and meta-analysis. Eur J Cardiothorac Surg. 2016;50(6):1010–8.
28. Thornton PC, Buggy DJ. Local anaesthetic wound infusion for acute postoperative pain: a viable option? Br J Anaesth. 2011;107(5):656–8.
29. Whooley BP, Law S, Murthy SC, et al. Analysis of reduced death and complication rates after esophageal resection. Ann Surg. 2001;233:338–344.
30. Yushang C, Zhiyong Z, Xiequn X. The analysis of changes and influencing factors of early postthoracotomy pulmonary Function. Chin Med Sci J. 2003;18:105–10.
31. Cense HA, Lagarde SM, De Jong K, Omloo JM, Busch OR, et al. Association of no epidural analgesia with postoperative morbidity and mortality after thoracic esophageal cancer resection. J Am Coll Surg. 2006;202(3):395–400. Mar.

UPPER GUT

Royal Australasian College of Surgeons

Does age affect oesophagectomy survival: a cohort study

Jin-soo Park,*† Hans Van der Wall,†‡ Catherine W. Kennedy§ and Gregory L. Falk*¶

*Department of Surgery, Concord Repatriation General Hospital, Sydney, New South Wales, Australia
†School of Medicine, The University of Notre Dame, Sydney, New South Wales, Australia
‡Department of Molecular Imaging, CNI Meadowbank, Sydney, New South Wales, Australia
§Department of Surgery, Strathfield Private Hospital, Sydney, New South Wales, Australia and
¶School of Medicine, The University of Sydney, Sydney, New South Wales, Australia

Key words
age, carcinoma oesophagus, oesophagectomy.

Correspondence
Dr Jin-soo Park, Department of Surgery, Concord Repatriation General Hospital, Suite 29, 12-18 Tryon Road, Lindfield, Sydney, NSW 2070, Australia. Email: jinsoopark91@gmail.com

J.-s. Park BMed, MD, MS; **H. Van der Wall** MBBS, PhD; **C. W. Kennedy** RMRA; **G. L. Falk** MBBS, FRACS, FACS.

Accepted for publication 3 December 2020.

doi: 10.1111/ans.16519

Abstract

Background: Curative oesophagectomy for oesophageal cancer is associated with considerable potential mortality. Surgeons are increasingly treating older patients presenting with oesophageal cancer as the population ages. The question remains as to the survival in an older population group, many of whom are not fit for combined multimodal therapy. This study aimed to assess the effect of age on overall survival and disease-free survival in patients undergoing curative oesophagectomy for cancer.

Methods: Patient data were analysed from a prospectively maintained database. Demographic, surgical and survival outcomes were compared between groups according to age less than 75 years or 75 and older.

Results: Oesophagectomy was performed in 351 patients between 1990 and 2019 (283 patients <75 years, 68 patients ≥75 years). There was a higher rate of neoadjuvant chemotherapy in the younger group (37.7% versus 7.4%; $P < 0.001$). The 30-day mortality between younger and older groups was similar (2.5% and 2.9%; $P = 0.827$). There was no statistical difference in 5-year survival rates (50.3% versus 38.6%; $P = 0.082$) or median survival (22.6 versus 19.3 months; $P = 0.053$) between groups. There was no statistical difference in 5-year disease-free survival (45.1% and 35.7%; $P = 0.180$).

Conclusion: Overall survival, disease-free survival and 30-day mortality rates in patients aged 75 years and older were not statistically different to their younger counterparts. On the basis of these results, older patients should not be precluded from consideration of potentially curative oesophagectomy on age alone, providing surgery may be performed at reasonable risk.

[Correction added on 4 January 2021 after first online publication: In the Results section of the abstract the correct sentence is: There was a higher rate of neoadjuvant chemotherapy in the younger group (37.7% versus 7.4%; $P < 0.001$).]

Introduction

The incidence of oesophageal cancer, particularly adenocarcinoma, is rising worldwide[1] and in Australia.[2] This may be related to increasing rates of obesity, smoking and gastro-oesophageal reflux disease.[3,4] Oesophagectomy remains a mainstay of curative management in this group of patients, although it may be associated with considerable mortality.[5] With ageing populations in Western countries and improvements in quality of life associated with this longevity, surgeons and oncologists can expect an increasing number of older patients presenting for consideration of curative treatment.[6]

Consideration of the risk and benefit of potentially morbid surgery in older patients remains unclear due to conflicting reports of survival data in contemporary literature and the influence of age on these outcomes. Advanced age has been identified as a negative prognostic survival indicator by some groups,[5] whereas others have demonstrated the safety of oesophagectomy in selected septuagenarian and octogenarian patients and comparable survival outcomes to younger patients.[7,8] Furthermore, these reports are based on series from other countries, with a scarcity of data describing survival outcomes in the elderly Australian patient.

This study aimed to describe the effect of age on overall survival and disease-free survival in patients undergoing curative

oesophagectomy for oesophageal cancer in a consecutive cohort treated by a single surgeon.

Methods

Patient selection and data collection

Data were extracted from a prospective oesophageal cancer database maintained by the senior author (GLF). Patients who underwent curative oesophagectomy for oesophageal cancer between January 1990 and October 2019 were identified and included in this study. Patients were not offered curative surgery if they were deemed unfit for surgery or if they had presence of metastatic disease on investigation. Patients were excluded if they underwent procedures in addition to oesophagectomy at the time of operation. Extracted data included baseline demographics, tumour location, histopathology, stage, perioperative outcomes and survival. Ethics approval was provided by Concord Hospital Human Research Ethics Committee (reference LNR/12/CRGH/248).

Neoadjuvant treatment was administered increasingly as evidence supporting its usage evolved, in the form of MAGIC protocol[9] chemotherapy for oesophageal adenocarcinoma and MRC protocol for oesophageal squamous cell carcinoma.[10]

Surgical management

All patients were operated and managed by one surgeon (GLF). Standard treatment for mid to lower oesophageal and oesophagogastric junction tumours was Ivor–Lewis oesophagectomy performed through a laparotomy and right thoracotomy. Transthoracic, en bloc mediastinal oesophagectomy with two-field lymphadenectomy was performed if it was thought all disease could be encompassed in surgical resection, including positive-appearing lymph nodes. A three-incisional McKeown procedure with an additional left cervical incision was infrequently used for tumours in the upper third of the oesophagus.

Standard follow-up was with the consultant surgeon (GLF), with clinical review at 3 months for 2 years, then 6 months until 5 years and then annually. The primary care physician was contacted where patients were remote or unable to attend review. Imaging was ordered 18 months following surgery or when indicated due to symptoms to assess evidence of recurrent disease. Staging was assessed by pathologists as per the 8th Edition of the American Joint Committee on Cancer guidelines,[11] and the database was completely restaged when the American Joint Committee on Cancer 8th Edition became current.

Statistical analysis

SPSS version 24.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Data were expressed as medians and ranges. Proportions of nominal and ordinal data were compared with the chi-squared test. Non-parametric continuous variables were compared with the Mann–Whitney *U*-test for two variables, or Kruskal–Wallis test for more than two variables. Survival data were plotted following the Kaplan–Meier method, and survival curves were analysed with the log-rank test. Multivariate analysis was performed using the Cox proportional hazard models to identify independent predictors of survival. The threshold for significance was $P < 0.05$.

Results

Population demographics

Oesophageal cancer was managed in 702 patients by the senior author between June 1990 and October 2019, of which a total of 395 patients underwent oesophagectomy with curative intent. Full data were unavailable for 39 patients who were lost to follow-up. A further five patients were excluded from analysis who underwent procedures in addition to oesophagectomy, such as right hemicolectomy or pulmonary resection. The remaining 351 patients formed the study cohort.

There were 283 patients younger than 75 years, and 68 patients were 75 years of age or older. The median age in the younger group was 64 years (range 29–74 years), and 78 years in the older group (range 75–87 years). The demographic and clinicopathological characteristics of the patients in the two groups are summarized in Table 1. Other histological types were 18 patients with high-grade dysplasia, four with undifferentiated carcinomas, three with melanomas and one with granular cell tumour.

Clinicopathological characteristics

Neoadjuvant chemotherapy (NACT) was utilized more frequently in the younger group: 106 (37.7%) in the <75-year-old group compared to five (7.4%) in those aged 75 years or older ($P < 0.001$).

Tumour characteristics were similar between the under 75 and over 75 groups (Table 1). The distribution of tumour site was similar between the two groups, although the most common site of oesophageal cancer was at the oesophagogastric junction in the younger group (44.7%) and lower third of the thoracic oesophagus in the older group (46.3%).

There were similar rates of adenocarcinoma between the younger and older groups, (70.6% and 64.7%, respectively; $P = 0.346$), as well as squamous cell carcinoma (22.7% and 25%, respectively; $P = 0.686$). The incidence of Barrett's oesophagus identified preoperatively was similar between the groups (31.8% and 38.2%, respectively; $P = 0.311$). Distribution of the degree of tumour differentiation was similar between the two groups. Resection margin status, presence of lymphovascular invasion and pathological TNM staging did not differ between the older and younger groups. Both age groups had similar proportions of patients with ≥30 lymph nodes harvested ($P = 0.898$).

Overall survival outcomes

The 30-day mortality of the overall cohort was 2.6% and was similar between the two age groups: seven (2.5%) in the <75-year-old group and two (2.9%) in the ≥75-year-old group ($P = 0.827$). In the whole cohort, median survival was 55.46 months (95% CI 27.78–83.14), and survival at 1, 2 and 5 years was 76.5%, 60.2% and 48%, respectively.

Table 1 Demographic and clinicopathological data

	Under 75 (n = 283)	75 and over (n = 68)	P-value
Age (median, range)	64 (29–74)	78 (75–87)	
Sex (male, female)	212, 71	51, 17	0.988
Neoadjuvant chemotherapy	106 (37.7%)	5 (7.4%)	<0.001*
Barrett's oesophagus	90 (31.8%)	26 (38.2%)	0.311
Tumour site			
Upper thoracic	6 (2.2%)	2 (3%)	0.703
Mid thoracic	43 (15.8%)	9 (13.4%)	0.637
Lower thoracic	102 (37.4%)	31 (46.3%)	0.181
Oesophagogastric junction	122 (44.7%)	25 (37.3%)	0.275
Histological type			
Adenocarcinoma	199 (70.6%)	44 (64.7%)	0.346
SCC	64 (22.7%)	17 (25%)	0.686
Other	19 (6.7%)	7 (10.3%)	0.315
Tumour grade			
Poorly differentiated	121 (48%)	26 (41.3%)	0.337
Moderately differentiated	111 (44%)	35 (55.6%)	0.101
Well differentiated	20 (7.9%)	2 (3.2%)	0.185
Resection margin status			
Not involved	256 (90.5%)	59 (86.8%)	0.240
Microscopically involved	21 (7.4%)	7 (10.3%)	0.303
Macroscopically involved	5 (1.8%)	2 (2.9%)	0.360
Lymphovascular invasion			
Present	95 (33.6%)	23 (33.8%)	0.460
Absent	188 (66.4%)	45 (66.2%)	0.460
Pathological TNM stage[†]			
Stage 0	14 (4.9%)	4 (5.9%)	0.359
Stage I	80 (28.3%)	20 (29.4%)	0.757
Stage II	56 (19.8%)	13 (19.1%)	0.922
Stage III	127 (44.9%)	29 (42.6%)	0.889
Stage IV	6 (2.1%)	2 (2.9%)	0.635
≥30 nodes removed	44 (15.5%)	11 (16.2%)	0.898
30-day mortality	7 (2.5%)	2 (2.9%)	0.827

[†]AJCC 8th Edition. *, significant result, AJCC, American Joint Committee on Cancer; SCC, squamous cell carcinoma.

Median survival in the <75-year-old group was 22.6 months (range 0.1–232.6), and 19.3 months in the ≥75-year-old group (range 0.1–184.6; P = 0.053). The Kaplan–Meier survival curve for overall survival between younger and older groups is shown in Figure 1. There was no difference in overall survival between the two age groups. Overall survival at 1, 2 and 5 years in the <75-year-old group was 78.7%, 63% and 50.3%, respectively. Overall survival at 1, 2 and 5 years in the ≥75-year-old group was 67.2%, 46.9% and 38.6%, respectively (P = 0.082).

Details of univariate analysis of overall survival are shown in Table 2. Male patients had a shorter median overall survival (21 months (range 0.1–220.3)) compared to female patients (31.6 months (range 0.5–232.6; P = 0.004)). Tumour histology affected overall survival, with adenocarcinoma having the lowest survival (P = 0.015), as did poorly differentiated tumours (P < 0.001). Presence of Barrett's oesophagus (P = 0.278), tumour location (P = 0.447), having ≥30 lymph nodes removed (P = 0.932) and NACT (P = 0.059) did not significantly affect overall survival.

Cox proportional hazard analysis identified histological grade (P < 0.001) and the number of nodes removed (P = 0.046) as independent prognostic factors. Age, male sex, tumour location, histological type, NACT and presence of Barrett's oesophagus did not predict overall survival on multivariate analysis (Table).

Disease-free survival outcomes

In the whole cohort, median disease-free survival was 25.84 months (95% CI 9.27–42.41), and disease-free survival at 1, 2 and 5 years was 68.6%, 51.6% and 43.3%, respectively.

Median disease-free survival in the <75-year-old group was 18.8 months (range 0.1–220.3), and 13.6 months in the ≥75-year-old group (range 0.1–184.6; P = 0.141). The Kaplan–Meier survival curve for disease-free survival between younger and older groups is shown in Figure 2. There was no difference in disease-free survival between the two age groups. Disease-free survival at 1, 2 and 5 years in the <75-year-old group was 69.6%, 52.9% and 45.1%, respectively. Disease-free survival at 1, 2 and 5 years in the ≥75-year-old group was 64.1%, 45.9% and 35.7%, respectively (P = 0.180).

Details of univariate analysis of disease-free survival are shown in Table 4. Male patients had a shorter median disease-free survival (15.3 months (range 0.1–220.3)) compared to female patients (22 months (range 0.5–210.8; P = 0.007)). Tumour histology

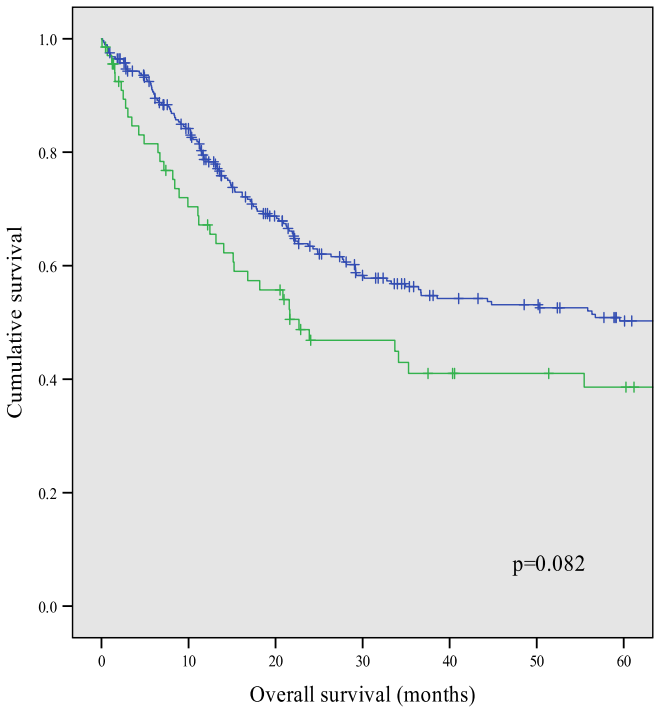


Fig 1. Age 75 years or older did not affect overall survival ($P = 0.082$). Age group: ——, <75 years old; ——, ≥75 years old; —|—, censored; —|—, censored.

Table 2 Univariate analysis of overall survival

	Overall survival (months, range)	*P*-value
Age		0.053
<75	22.6 (0.1–232.6)	
≥75	19.3 (0.1–184.6)	
Sex		0.004*
Male	21 (0.1–220.3)	
Female	31.6 (0.5–232.6)	
Tumour location		0.447
Upper thoracic	45.8 (1.5–122.3)	
Mid thoracic	26.8 (0.5–232.6)	
Lower thoracic	18.2 (0.1–218.7)	
Oesophagogastric junction	21.6 (0.1–220.3)	
Histological type		0.015*
Adenocarcinoma	19.3 (0.1–220.3)	
SCC	23.9 (0.5–232.6)	
Other	41.9 (3.6–206.4)	
Tumour grade		<0.001*
Poorly differentiated	14.9 (0.1–203.2)	
Moderately differentiated	22.2 (0.3–232.6)	
Well differentiated	91.5 (3–218.7)	
Number of nodes removed		0.932
<30 nodes removed	21.8 (0.1–232.6)	
≥30 nodes removed	25 (0.8–176.5)	
NACT		0.059
NACT	23.3 (0.1–232.6)	
Surgery only	19.9 (0.8–191.7)	
Barrett's oesophagus		0.278
No Barrett's	22.3 (0.4–232.6)	
Barrett's	20.8 (0.1–218.7)	

*, significant result, NACT, neoadjuvant chemotherapy; SCC, squamous cell carcinoma.

Table 3 Multivariate analysis of predictors of survival

	Hazard ratio (95% confidence interval)	*P*-value
Age ≥75	1.01 (0.99–1.02)	0.272
Male sex	1.31 (0.93–1.85)	0.119
Tumour location (lower)	1.25 (0.90–1.74)	0.176
Histological type (SCC)	1.45 (0.97–2.17)	0.074
Tumour grade (poorly differentiated)	1.97 (1.43–2.72)	<0.001*
Number of nodes removed ≥30	0.62 (0.38–0.99)	0.046*
NACT	1.03 (0.72–1.47)	0.864
Barrett's oesophagus	1.36 (0.96–1.94)	0.085

*, significant result, NACT, neoadjuvant chemotherapy; SCC, squamous cell carcinoma.

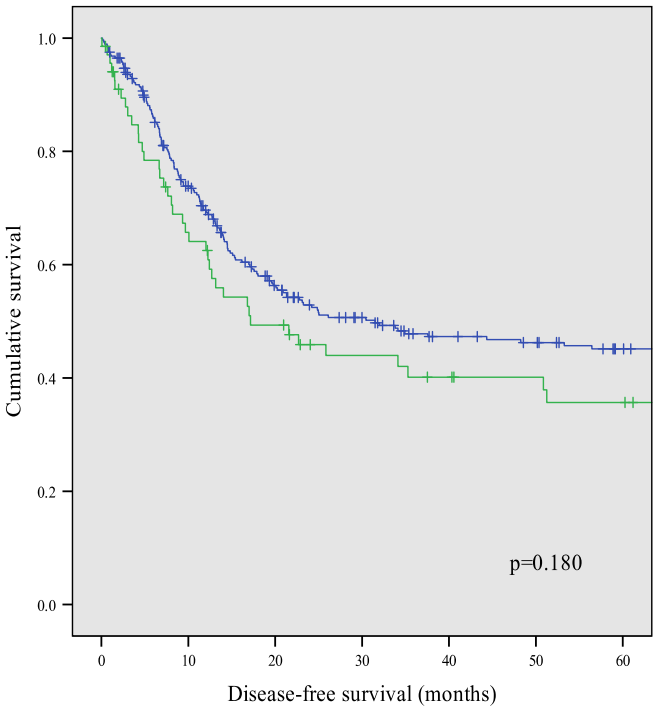


Fig 2. Age 75 years or older did not affect disease-free survival ($P = 0.180$). Age group: ——, <75 years old; ——, ≥75 years old; —|—, censored; —|—, censored.

affected disease-free survival, with adenocarcinoma having the fastest recurrence time ($P = 0.013$), as did poorly differentiated tumours ($P < 0.001$). NACT, compared with surgery alone, trended towards improving disease-free survival (20 versus 13.8 months; $P = 0.050$). The presence of Barrett's oesophagus ($P = 0.452$), tumour location ($P = 0.664$) and having ≥30 lymph nodes removed ($P = 0.735$) did not significantly affect time until disease recurrence.

Discussion

There is growing evidence in the literature to support the selection of elderly patients for curative oesophagectomy in the treatment of oesophageal cancer, with studies reporting survival outcomes as

Table 4 Univariate analysis of disease-free survival

	Disease-free survival (months, range)	*P*-value
Age		0.141
<75	18.8 (0.1–220.3)	
≥75	13.6 (0.1–184.6)	
Sex		0.007*
Male	15.3 (0.1–220.3)	
Female	22 (0.5–210.8)	
Tumour location		0.664
Upper thoracic	31.5 (4.9–206.4)	
Mid thoracic	19.8 (0.5–210.8)	
Lower thoracic	15.3 (0.1–218.7)	
Oesophagogastric junction	17.3 (0.1–220.3)	
Histological type		0.013*
Adenocarcinoma	14.7 (0.1–220.3)	
SCC	19.3 (0.5–210.8)	
Other	41.9 (2.3–206.4)	
Tumour grade		<0.001*
Poorly differentiated	11.7 (0.1–203.2)	
Moderately differentiated	20.2 (0.3–220.3)	
Well differentiated	91.5 (3–218.7)	
Number of nodes removed		0.735
<30 nodes removed	17.3 (0.1–220.3)	
≥30 nodes removed	17.5 (0.8–176.5)	
NACT		0.05
NACT	20 (0.1–220.3)	
Surgery only	13.8 (0.8–191.9)	
Barrett's oesophagus		0.452
No Barrett's	17.9 (0.4–220.3)	
Barrett's	15.9 (0.1–218.7)	

*, significant result, NACT, neoadjuvant chemotherapy; SCC, squamous cell carcinoma.

favourable as those in younger patients.[12–14] The present study evaluates the effect of age on survival outcomes following curative oesophagectomy for oesophageal cancer in an Australian tertiary referral unit. In terms of 30-day mortality, overall survival and disease-free survival, patients aged 75 years and over have similar outcomes to younger patients.

Patients younger than 75 years had a significantly higher rate of NACT than the older group (37.7% versus 7.4%; $P < 0.001$). This may have created a down-staging bias in the study for the under 75-year-old group. The fact that this did not alter the outcome of the end points of the study indicates that at best, the effect was modest.

We report 5-year survival rates of 50.3% in the <75-year-old group and 38.6% in the ≥75-year-old group, although this did not have statistical significance ($P = 0.082$). This is similar to results reported in other studies that also conclude that advanced age does not negatively impact overall survival. Fang *et al*. did not demonstrate a difference in overall or cause-specific mortality rates in patients aged 70 years or older undergoing three-field oesophagectomy for cancer. They reported 5-year survival rates of 48.1% in the younger group compared to 40.9% in the older group.[15] Ellis *et al*. reported no difference in their 5-year survival rates between their groups younger than 70 years (22.4%) and older than 70 years (24.1%),[12] as did Thomas *et al*. when comparing 5-year survival between their groups younger than 70 years (18.9%) and 70 years and older (17%), although this study is an outlier for lower curve rates.[13] Likewise, Ruol *et al*. demonstrated similar 5-year survival rates in patients younger than 70 years and those aged 70 years and older (33.6% and 35.4%, respectively).[14] Bonavina *et al*. found 5-year survival rates of around 35% in patients undergoing oesophagectomy when grouped by age as <65 and ≥65 years to be similar.[16] O'Grady *et al*. concluded in an Australian cohort that age did not significantly affect long-term survival when comparing patients aged under 60, 60–69 and older than 70 years, although the 5-year survival figures were not reported.[17] Previous studies have even demonstrated similar long-term survival outcomes in patients aged 80 years and older when compared with younger patients undergoing oesophagectomy for cancer. Alexiou *et al*. reported comparable 5-year survival rates in three age groups: under 70, 70–79 and 80 years and older (25.1%, 21.2% and 19.8%).[18] Morita *et al*. did not demonstrate a significant difference in cause-specific survival in three different age groups: >80, 70–79 and ≤70 years.[7] However, these studies, similar to the current study, have sample sizes that are not large enough to detect significant differences.

In contrast, Moskovitz *et al*. demonstrated significantly worse perioperative mortality and survival in patients aged 80 years and over compared with those aged 50–79 years undergoing oesophagectomy for cancer.[19] McLoughlin *et al*. demonstrated a significant difference in overall survival in patients younger than 70 years compared with their older counterparts, although they did not report 5-year survival rates.[20]

We report a 30-day mortality rate of 2.6%, with similar rates between younger and older age groups (2.5% versus 2.9%; $P = 0.827$). These mortality rates are in keeping with 30-day mortality rates reported in the literature, which range from 1.25% to 7.9% in patients younger than 70 years and 3.3–7.2% in patients aged 70 years and older.[5,7,12,13] These studies similarly did not find 30-day mortality was different between younger and older patient groups following oesophagectomy for cancer. Koppert *et al*. reported a statistically significant increase in 30-day mortality rate with age when comparing patients aged <70 years with those aged 70 years or more (4.7% and 11.9%),[21] unlike our series. This was also at a lower age group than the elderly in our series and may reflect a selection effect.

There has been a decreasing trend in 30-day mortality rates over time. This has generally been accepted to be a product of refinement in patient selection and surgical technique in oesophagectomy, as well as improved perioperative patient care by early recovery after surgery protocols. Post-operative epidural analgesia improves pain control and confers greater function in pulmonary mechanics in the immediate post-operative setting, which in turn improves morbidity and mortality.[22] These results were achieved in a specialized institution for oesophageal diseases by a single surgeon with a moderate volume of oesophageal surgery. It is recognized that oesophagectomies have lower morbidity and mortality when performed in higher volume centres.[23,24]

The current report has a 5-year disease-free survival rates of 45.1% in the <75-year group and 35.7% in the ≥75-year group, with age not affecting disease-free survival ($P = 0.180$). Conflicting

reports exist as to the effect of age on disease-free survival. Lee *et al*. found that in patients with completely resected oesophageal cancer, disease-free survival was not affected by age in multivariate analysis with adjustment for advanced pathological stage differences.[25] In contrast, Pultrum *et al*. report significantly more recurrences in patients younger than 70 years compared to their older counterparts (58% versus 42%).[26]

A limitation of this study is its sample size. With 351 patients, the present study is underpowered to detect a true difference in survival. The single-surgeon experience limits the ability to generalize results.

An advantage of this study was the prospective nature of data collection and standardized selection and surgery. Neoadjuvant therapy was introduced during this study but surgical lymphadenopathy and en bloc mediastinal resection have remained stable. This study covers three decades and, during this time, there have been improvements in the investigation and management of oesophageal cancer that likely result in better preoperative staging, and altered selection likely results in the treatment of less advanced disease.

Conclusion

The present study reports that overall survival, 30-day mortality rates and disease-free survival in patients aged 75 years and over were not statistically different to their younger counterparts. According to the results of the present study, older patients should not be precluded from consideration of potentially curative oesophagectomy on the basis of age alone, providing surgery may be performed at reasonable risk.

Author Contributions

Jin-soo Park: Data curation; formal analysis; writing-original draft; writing-review and editing. **Hans Van der Wall:** Formal analysis; writing-review and editing. **Catherine W. Kennedy:** Data curation; resources; supervision. **Gregory L. Falk:** Conceptualization; data curation; writing-review and editing.

Conflicts of interest

None declared.

References

1. Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends – an update. *Cancer Epidemiol. Biomarkers Prev.* 2016; **25**: 16–27.
2. Stavrou EP, McElroy HJ, Baker DF, Smith G, Bishop JF. Adenocarcinoma of the oesophagus: incidence and survival rates in New South Wales, 1972-2005. *Med. J. Aust.* 2009; **191**: 310–4.
3. Whiteman DC, Sadeghi S, Pandeya N *et al*. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. *Gut* 2008; **57**: 173–80.
4. Pera M, Manterola C, Vidal O, Grande L. Epidemiology of esophageal adenocarcinoma. *J. Surg. Oncol.* 2005; **92**: 151–9.
5. Poon RT, Law SY, Chu KM, Branicki FJ, Wong J. Esophagectomy for carcinoma of the esophagus in the elderly: results of current surgical management. *Ann. Surg.* 1998; **227**: 357–64.
6. Smith GL, Smith BD, Buchholz TA *et al*. Patterns of care and locoregional treatment outcomes in older esophageal cancer patients: the SEER-Medicare Cohort. *Int. J. Radiat. Oncol. Biol. Phys.* 2009; **74**: 482–9.
7. Morita M, Egashira A, Yoshida R *et al*. Esophagectomy in patients 80 years of age and older with carcinoma of the thoracic esophagus. *J. Gastroenterol.* 2008; **43**: 345–51.
8. Sabel MS, Smith JL, Nava HR, Mollen K, Douglass HO, Gibbs JF. Esophageal resection for carcinoma in patients older than 70 years. *Ann. Surg. Oncol.* 2002; **9**: 210–4.
9. Cunningham D, Allum WH, Stenning SP *et al*. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N. Engl. J. Med.* 2006; **355**: 11–20.
10. MRCOC. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 2002; **359**: 1727–33.
11. Rice TW, Patil DT, Blackstone EH. 8th Edition AJCC/UICC staging of cancers of the esophagus and esophagogastric junction: application to clinical practice. *Ann. Cardiothorac. Surg.* 2017; **6**: 119–30.
12. Ellis FH, Williamson WA, Heatley GJ. Cancer of the esophagus and cardia: does age influence treatment selection and surgical outcomes? *J. Am. Coll. Surg.* 1998; **187**: 345–51.
13. Thomas P, Doddoli C, Neville P *et al*. Esophageal cancer resection in the elderly. *Eur. J. Cardiothorac. Surg.* 1996; **10**: 941–6.
14. Ruol A, Portale G, Zaninotto G *et al*. Results of esophagectomy for esophageal cancer in elderly patients: age has little influence on outcome and survival. *J. Thorac. Cardiovasc. Surg.* 2007; **133**: 1186–92.
15. Fang W, Igaki H, Tachimori Y, Sato H, Daiko H, Kato H. Three-field lymph node dissection for esophageal cancer in elderly patients over 70 years of age. *Ann. Thorac. Surg.* 2001; **72**: 867–71.
16. Bonavina L, Incarbone R, Saino G, Clesi P, Peracchia A. Clinical outcome and survival after esophagectomy for carcinoma in elderly patients. *Dis. Esophagus* 2003; **16**: 90–3.
17. O'Grady G, Hameed AM, Pang TC *et al*. Patient selection for oesophagectomy: impact of age and comorbidities on outcome. *World J. Surg.* 2015; **39**: 1994–9.
18. Alexiou C, Beggs D, Salama FD, Brackenbury ET, Morgan WE. Surgery for esophageal cancer in elderly patients: the view from Nottingham. *J. Thorac. Cardiovasc. Surg.* 1998; **116**: 545–53.
19. Moskovitz AH, Rizk NP, Venkatraman E *et al*. Mortality increases for octogenarians undergoing esophagogastrectomy for esophageal cancer. *Ann. Thorac. Surg.* 2006; **82**: 2031–6.
20. McLoughlin JM, Lewis JM, Meredith KL. The impact of age on morbidity and mortality following esophagectomy for esophageal cancer. *Cancer Control* 2013; **20**: 144–50.
21. Koppert LB, Lemmens VEPP, Coebergh JWW *et al*. Impact of age and co-morbidity on surgical resection rate and survival in patients with oesophageal and gastric cancer. *Br. J. Surg.* 2012; **99**: 1693–700.
22. Lun Tsui S, Law S, Fok M *et al*. Postoperative analgesia reduces mortality and morbidity after esophagectomy. *Am. J. Surg.* 1997; **173**: 472–8.
23. Casson AG, van Lanschot JJB. Improving outcomes after esophagectomy: the impact of operative volume. *J. Surg. Oncol.* 2005; **92**: 262–6.
24. Chang AC, Birkmeyer JD. The volume–performance relationship in esophagectomy. *Thorac. Surg. Clin.* 2006; **16**: 87–94.
25. Lee PC, Mirza FM, Port JL *et al*. Predictors of recurrence and disease-free survival in patients with completely resected esophageal carcinoma. *J. Thorac. Cardiovasc. Surg.* 2011; **141**: 1196–206.
26. Pultrum BB, Bosch DJ, Nijsten MWN *et al*. Extended esophagectomy in elderly patients with esophageal cancer: minor effect of age alone in determining the postoperative course and survival. *Ann. Surg. Oncol.* 2010; **17**: 1572–80.

review

Eur Surg (2020) 52:110–117
https://doi.org/10.1007/s10353-019-00627-x

european surgery
ACA Acta Chirurgica Austriaca

The real risk of nodal disease in T1 oesophageal adenocarcinoma

A systematic review

David P. Mitchell · Sashi Yeluri · Hans Van der Wall · Gregory L. Falk

Received: 12 December 2019 / Accepted: 23 December 2019 / Published online: 17 February 2020

Summary
Background Lymph node status is regarded as an important factor in the prognosis of oesophageal cancer. T1 oesophageal adenocarcinoma management has to include endoscopic management as part of the algorithm. We reviewed the literature to assess the true risk of lymph node metastasis in patients with T1 oesophageal adenocarcinoma.
Methods Medline, Embase, PubMed and Cochrane where searched for manuscripts in English reviewing lymph node metastasis in superficial (T1) oesophageal adenocarcinoma. The main outcome was probability of lymph node metastasis in T1a and T1b oesophageal adenocarcinoma. Secondary outcome was the rate of lymph node metastasis of submucosal involvement of T1b (SM1, SM2 and SM3).
Results There were 38 studies identified. 22 studies were excluded due to low lymph node yield (<15) or insufficient statistical analysis. For the 16 remaining studies, a total of 1382 cases were included: T1a adenocarcinoma (533 patients) with 11 (2%) node positive and T1b adenocarcinoma (849 patients) with 189 (22%) node positive. Subgroup analysis of T1b lesions was available in 8 reports (365 patients). Node positivity for SM1, SM2 and SM3 was 19.9%, 20.2% and 32.9%, respectively.
Conclusion T1a disease on endoscopic mucosal resection (EMR) demonstrates a 2% nodal metastasis rate, T1b disease a rate of 22%. T1a disease may be safely treated by EMR. T1a disease appears suitable for endoscopic therapy; however, T1b disease presents a high rate of nodal metastasis.

Keywords Early oesophageal cancer · Depth of invasion · Submucosa · Node metastasis

D. P. Mitchell, BSc MBBS FRACS · S. Yeluri, MBBS FRCS · G. L. Falk, MBBS FRCS FRACS (✉)
Concord Hospital, Hospital Road, 2129 Concord, NSW, Australia
sydney.heartburn@gmail.com

D. P. Mitchell, BSc MBBS FRACS
david_mitchell@live.com.au

S. Yeluri, MBBS FRCS
sashi_yeluri@yahoo.com

H. Van der Wall, PhD, FRACP
CNI medical imaging, Meadowbank, New South Wales, Australia
hvanderwall@gmail.com

G. L. Falk, MBBS FRCS FRACS
Suite 29, 12 Tryon Road, 2070 Lindfield, NSW, Australia

Main novel aspects

- An adequate appreciation of the risk of nodal metastasis in early oesophageal cancer has not been readily available.
- The likely chance of the presence of nodal metastatic disease has been evaluated for early oesophageal cancer in systematic review.
- The assesment of patients for safe endoscopic therapy for early adenocarcinoma of the oesophagus will be enhanced by this data.

Introduction

The treatment paradigm for management of early oesophageal adenocarcinoma has changed over the past 15 years, with a shift towards endoscopic management and away from oesophagectomy [1]. In T1a and high-grade dysplasia, endoscopic mucosal resection (EMR) has been widely regarded as the standard of care, with some bodies [1] recommending it for T1a and selected T1b disease. Whilst endoscopic management has a major role in the treatment of early dis-

ease, it is limited due to reliance on radiological and endoscopic techniques for prediction of lymph node status. It is well established that lymph node status is the most important prognostic factor for early oesophageal adenocarcinoma and cannot be treated by endoscopy. Tumour depth and nodal status are critical for adequate staging of disease to allocate appropriate treatment. Despite the shift in treatment paradigm, the rate of lymph node positivity is reported variably in the literature for T1a and particularly T1b disease, making it difficult to appropriately recommend treatment pathways. This study aimed to clarify the risk of lymph node disease in T1a and T1b oesophageal adenocarcinoma.

Methods

This systematic review was presented according to the PRISMA statement where appropriate. Electronic searches were performed in PubMed, Embase, Medline and the Cochrane library in September 2016. The strategies combined search terms for early oesophageal adenocarcinoma and lymph node status. Results were filtered for English studies only. Exclusion criteria included average lymph node yield for the study ≥15 [2]. Given the role of lymph node status and the association between survival and adequate lymphadenectomy, it was resolved to include only those studies that demonstrated adequate lymphadenectomy so as not to underestimate the rate of nodal involvement. The second exclusion criterium was treatment with neoadjuvant chemotherapy or chemoradiotherapy, which may negatively affect nodal positivity results [4, 5].

Abstracts were reviewed and full texts obtained. Each article was reviewed independently by two authors. Both screened full-text papers and bibliographies for other possible references for inclusion. This systematic review was registered with Prospero prior to commencement.

Statistical analysis was calculated utilising SPSS Statistics version 22 (IBM, Sydney, Australia). The primary outcome measure was the prevalence of lymph node metastases for T1a and T1b tumours. Secondary outcome measure was the prevalence of lymph node metastases for each subclass of submucosal invasion.

Results

Following abstract screening, 38 full-text journal articles were identified and 16 studies met the criteria (Table 1). A total of 22 papers were excluded, 7 for insufficient lymph node yield, of which 2 were the largest series based on the American National Cancer Database. Other exclusions were for lack of data analysis, no adenocarcinoma within the series or lymph node yield not reported. Subgroup analysis of T1b lesions was available in 8 articles, described as submucosal 1 (SM1), submucosal 2 (SM2) and submucosal 3 (SM3). The operative approach utilised between each study was quite variable and generally involved combinations of transhiatal, Ivor Lewis (two-stage) or McKeown (3 Stage) oesophagectomy.

Definition of early oesophageal adenocarcinoma:

All journal articles used the same definition for T1a and T1b, which was consistent with current TNM staging (Figs. 1 and 2). T1a was defined as invading the

Table 1 Clinicopathological nodal findings in T1 adenocarcinoma

Author	Year	Country	Average lymph node yield	Total no. of patients	T1a	T1b	Total lymph node positive (%)	T1a (%)	T1b (%)
Gockel et al. [6]	2009	Germany	16	29	14	15	4 (13.8)	1 (7.1)	3 (20)
Stein et al. [7]	2005	Germany	24	157	70	87	18 (11.4)	0 (0)	18 (20.7)
Holscher et al. [8]	2011	Germany	27	121	55	66	16 (13.2)	0 (0)	16 (24.2)
Sepesi et al. [9]	2010	USA	22	54	25	29	9 (16.7)	0 (0)	9 (31.0)
Nigro et al. [10]	1999	USA	41	27	15	12	7 (25.9)	1 (0)	6 (50.0)
Griffin et al. [11]	2011	UK	25	96	31	65	8 (8.3)	0 (0)	8 (12.3)
Badreddine et al. [12]	2010	USA	15	80	0	80	14 (17.5)	–	14 (17.5)
Manner et al. [13]	2015	Germany	27	29	0	29	3 (10.3)	–	3 (10.3)
Leers et al. [14]	2011	USA	34	126	75	51	12 (9.5)	1 (1.3)	11 (21.6)
Gertler et al. [15]	2014	Germany	25	224	71	153	27 (12.1)	0 (0)	27 (17.6)
Lee et al. [16]	2013	Canada	>28	258	122	136	42 (16.2)	7 (5.7)	35 (25.7)
Nentwich et al. [17]	2014	USA	21	37	0	37	10 (27.0)	–	10 (27.0)
Bogoevski et al. [18]	2011	Germany	>15	53	25	28	9 (16.9)	0 (0)	9 (32.1)
Hagen et al. [19]	2001	USA	48	32	16	16	6 (18.8)	1 (6.3)	5 (31.2)
Molena et al. [20]	2017	USA	27	23	0	23	6 (26.0)	–	6 (26.1)
Bollschweiler et al. [21]	2006	Germany	30	36	14	22	9 (25.0)	0 (0)	9 (40.9)
Total	–	–	–	*1422*	*533*	*849*	*200 (14.1)*	*11 (2.06)*	*189 (22.2)*

Table 2 T1b Clinicopathological data on submucosal lymph node positivity

Author	Year	Number T1b patients	SM1 node positive (%)	SM2 node positive (%)	SM3 node Positive (%)
Bollschweiler et al. [21]	2006	22	2 (22.2)	0 (0)	7 (77.8)
Goekel et al. [6]	2009	15	1 (12.5)	1 (50.0)	1 (20.0)
Holscher et al. [8]	2011	66	2 (8.7)	2 (13.3)	12 (35.7)
Sepesi et al. [9]	2010	29	3 (21.4)	4 (36.4)	2 (50.0)
Griffin et al. [11]	2011	65	5 (22.7)	1(4.1)	2 (10.5)
Badreddine et al. [12]	2010	80	4 (12.9)	5 (21.7)	5 (19.2)
Leers et al. [14]	2011	51	4 (21.1)	1 (11.1)	6 (26.0)
Nentwich et al. [17]	2014	37	3 (37.5)	2 (25.0)	5 (23.8)
Total	–	*365*	*24 (17.9)*	*16 (16.7)*	*40 (29.6)*

mucosa and muscularis mucosa without submucosal involvement. T1b was defined as involving the submucosa but not invading the muscularis propria. Further subclassification of the T1b lesions based on the degree of submucosal involvement was consistently defined in all 8 articles as involving the upper third, middle third or lower third of the submucosa.

Incidence of node positivity in T1a and T1b

A total of 16 articles (Table 1) were included in the node positivity analysis for T1a and T1b lesions. There was a total of 1422 patients: T1a in 533 and 849 patients had T1b lesions. There was a total of 200 patients with positive lymph nodes. Patients were node positive in 11 of the T1a group (11/533) which equated to a 2.06% lymph node positivity rate. Within the T1b group there were 189 patients with node positivity (189/849), giving a 22.26% lymph node positive rate. The mean lymph node yield was 25.6 ± 8.8.

Subgroup analysis T1b

The 8 studies included 365 patients with a mean lymph node yield of 23.8 ± 6.6. There were 134 SM1 patients, with 24 patients with positive lymph nodes (19.9%). SM2 was similar, with 16 of 96 patients lymph node positive (20.2%). Lymph node involvement was present in stage SM3 with 40 of 135 patients positive (32.9%; Tab. 2).

Decision tree

A case may be made for endoscopic management of T1b disease that has superficial (SM1) or intermediate (SM2) submucosal involvement, but not for deep submucosal (SM3) involvement. The rate of lymph node metastasis for deep involvement is a mean of 32.9% (95% CI 18.2–45.0%), which is significantly higher than for SM1 or SM2 disease ($p = 0.001$) with no significant difference between SM1 and SM2 disease (Fig. 3).

Discussion

The rate of lymph node involvement in early oesophageal adenocarcinoma (EAC) (Fig. 4) has long been quoted variably between 0 and 30%. With such variability in lymph node metastasis, clinical decision making is difficult. Current management approaches for early oesophageal adenocarcinoma have shifted from traditional oesophagectomy to selective minimally invasive procedures including EMR and, for some, endoscopic submucosal dissection (ESD), making such prediction vital. Central bodies including the NCCN recommend EMR for T1a and endoscopic management for selected T1b tumours [1]. The main limitation of endoscopic therapies is the risk of nodal metastasis and the difficulty of practically identifying their presence in the individual. This review attempts to quantify the risk of error in assessment of nodal status in clinical management.

Many reports are mixed SCC, with low-volume early adenocarcinoma. The largest series from the USA, based on the National Cancer Database, have low lymph node yield (Fig. 5) with a median of 10, which was not considered an adequate sample by Samson et al. [22], who demonstrated that only 29% of the US National Cancer Database patients had 15 or more lymph nodes resected. They indicated that 20–25 resected lymph nodes may be the optimal number to improve survival. Lymph node count is known to have an influence on survival and particularly a negative lymph node yield [23]. Greenstein et al. [24] demonstrated that in node-negative disease, 5-year survival improved with increasing number of nodes resected and suggested that greater than 18 lymph nodes should be resected. Initially, the ISDE and currently the NCCN [1] and AUGIS recommend the resection of 15 lymph nodes as a consensus number, but it seems to represent a compromise, as survival seems to improve with greater numbers resected. Peyre et al. [25] reviewed 2303 oesophageal resection cases and demonstrated that the number of lymph nodes resected was an independent predictor of survival and demonstrated that survival improved to a minimum of 23 lymph nodes removed. There has been a suggestion that the number of lymph

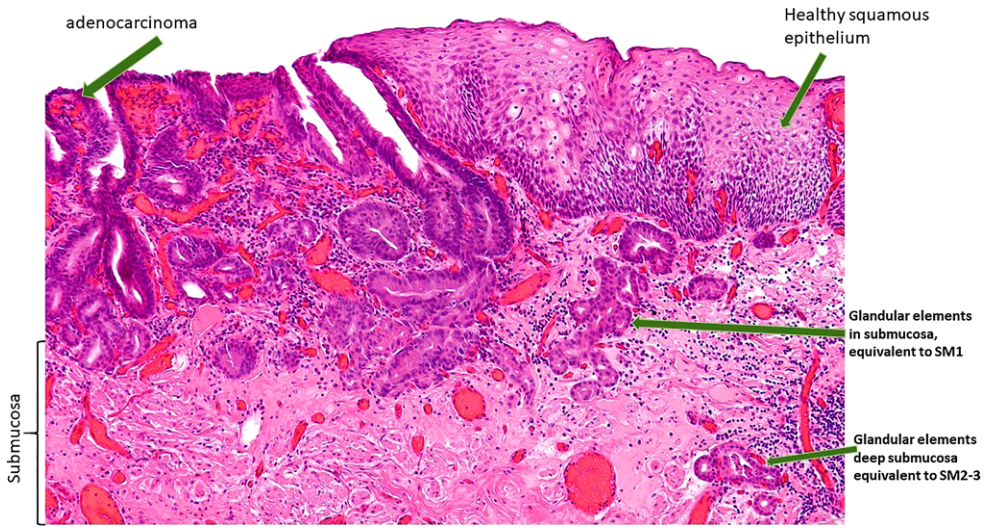


Fig. 1 Oesophageal adenocarcinoma at the squamous junction. Adenocarcinoma shown in the upper left with a *dark blue* colouration. Normal squamous epithelium is found in the upper right. H & E; *SM1* invasion of the superficial third of the submucosa, *SM2* invasion of the mid third of submucosa, *SM3* invasion of the deep third of submucosa but not muscularis propria

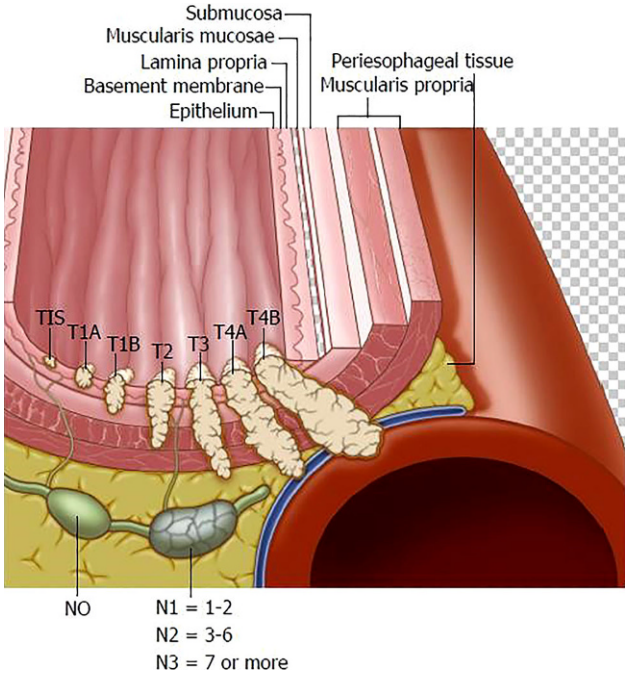


Fig. 2 Representation of the tumour stages: oesophageal adenocarcinoma staging according to AJCC 8th edition [46]

nodes required is dependent on the stage of disease. Rizk et al. [26] reviewed 4627 patients from the Worldwide Esophageal Cancer Collaboration and found that moderate to poorly differentiated and node-positive disease had improved 5-year survival with increasing lymphadenectomy. They recommended 10–12 lymph nodes removed for T1a, 15–22 lymph nodes for T2 disease and 31–42 for T3/T4 disease pending histological type. For N0M0 disease and nodal positivity (1–6), they recommended removal of 10 for T1, 15 for T2 and 29–50 for T3/4. On the basis of present data, a cut-off for analysis in this article of 15 resected nodes was taken.

The role of endoscopic therapy is dependent upon preoperative staging. The main limitation of endoscopic therapy is the lack of lymph node pathology. Whilst depth of invasion is one key to the likelihood of lymph node metastases, others factors have been demonstrated to increase the risk of nodal disease, including the presence of lymphovascular invasion, tumour size, and degree of differentiation [26]. This makes the risk of metastasis to lymph nodes less predictably related to T stage alone. A variety of modalities are used to assess lymph node disease, including computed tomography (CT), positron-emission tomography (PET) and endoscopic ultrasound (EUS), all with varying degrees of specificity and sensitivity, which are generally not adequate for clinical use.

EUS has been demonstrated to be 80–90% accurate for assessing T staging of oesophageal tumours; however, evidence suggests it has limitations in distinguishing T1a from T1b. Thus, it has been replaced by endoscopic resection (ER) as the preferred staging modality and for possible management of EAC. EUS's greatest use is for the staging of nodal metastases as it is the most accurate method, with overall accuracy ranging from 75% based on size, shape, borders and hypoechoic structure of the node [27]. Improved accuracy, sensitivity and specificity to 90% can be achieved with the addition of fine needle aspiration (FNA). FNA cannot be performed if it requires transgression of a lesion. Sandha et al. [28] compared all three modalities and found an overall accuracy of 81% for EUS, 69% for CT and 56% for PET. A meta-analysis [29] reviewing the utility of CT for nodal staging of oesophageal cancer found that regional nodes had a pooled sensitivity of 0.50 and specificity 0.83. Given the low sensitivity, the main role of CT is the assessment of metastatic disease. PET is also demonstrated to have low sensitivity (0.50) but good specificity (0.85). Cuellar et al. [29] demonstrated a sensitivity and positive predictive value of 0% for EAC. Given the poor sensitivity, the role of PET in staging EAC is questionable. The assessment of nodal disease in EAC appears inadequate and at best maybe 91%

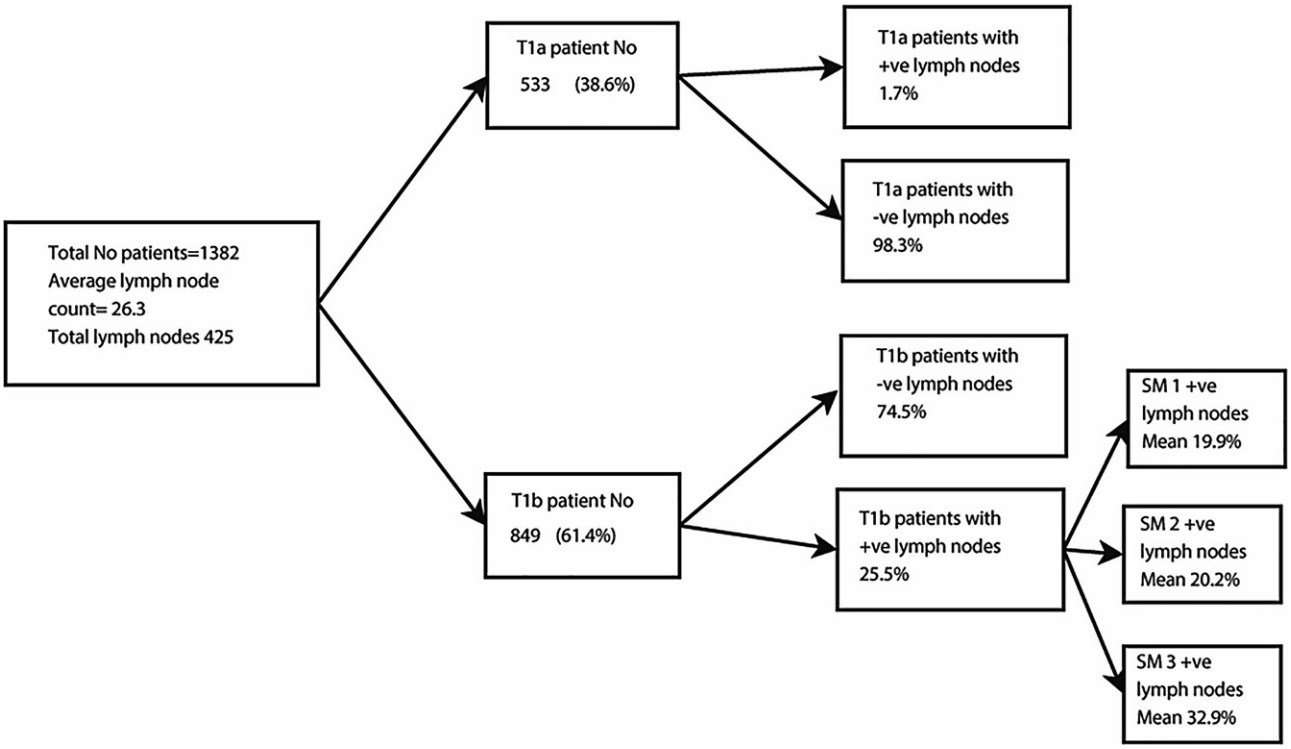


Fig. 3 Decision tree analysis on the grouped datasets. The tree diagram demonstrates lymph node positivity for T1 grade oesophageal adenocarcinoma for stages T1a and T1b. There is further analysis of the T1b cases by submucosal depth of the primary tumour. Note the difference between the SM1 and SM2 versus SM3 subtypes in terms of lymph node positivity. *SM1* Invasion of the superficial third of the submucosa, *SM2* invasion of the mid third of submucosa, *SM3* invasion of the deep third of submucosa but not muscularis propria

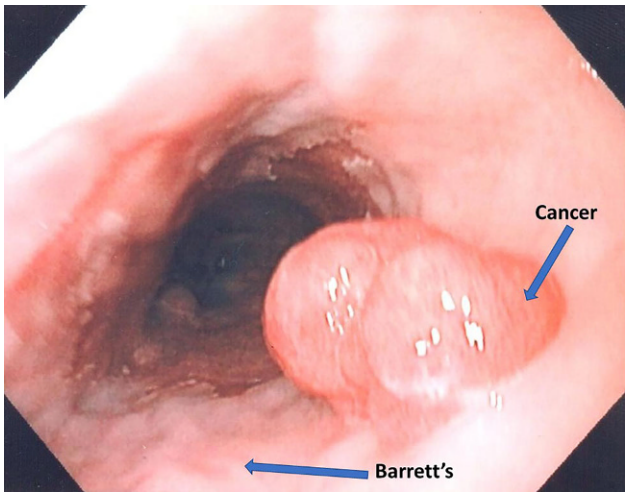


Fig. 4 Endoscopic view of early oesophageal cancer in Barrett's oesophagus

with EUS and biopsy. The 10% inaccuracy becomes more significant considering the high rate of cure in early lesions.

Endoscopic resection is a relatively safe procedure. Ell et al. [30] demonstrated effective endoscopic treatment that in 100 consecutive patients with a 99% local remission with no severe complications and a 98% 5-year survival with no cancer deaths. Recurrent or metachronous carcinomas were found in 11% of patients at 36.7 months. Piecemeal resection, long-segment Barrett's oesophagus and multifocal neoplasia were higher risks for recurrence. Extended study from the same group [31], with an expanded patient volume of 1000 patients, and a 52% long segment Barretts oesophagus rate, achieved a complete response in 96.3%, with 12 patients requiring surgery. Metachronous or local recurrence occurred in 14.5% patients, with major complications in 1.5% of patients. The endoscopic series of Pech et al. [32] demonstrated a 93.8% survival for T1 disease at 56.6 months. Manner et al. [33] demonstrated that endoscopic resection in patients unsuitable for surgery developed recurrent or metachronous lesions in 28% of patients at 5 years. The overall survival was 66% at 5 years, with no cancer-related deaths. Endoscopic resection for early disease appears greatly effective, so adequate clinical choice is dependent upon node status diagnosis.

The risk of occult synchronous cancers in Barrett's oesophagus is significant, with 40% found in pathological studies [34]. Pech et al. [32] showed in 1000 patients that good results can be achieved for T1a lesions, as series had 52% long-segment Barrett's and a metachronous and local recurrence rate of 14.5%. However, if endoscopic resection is used to treat T1a

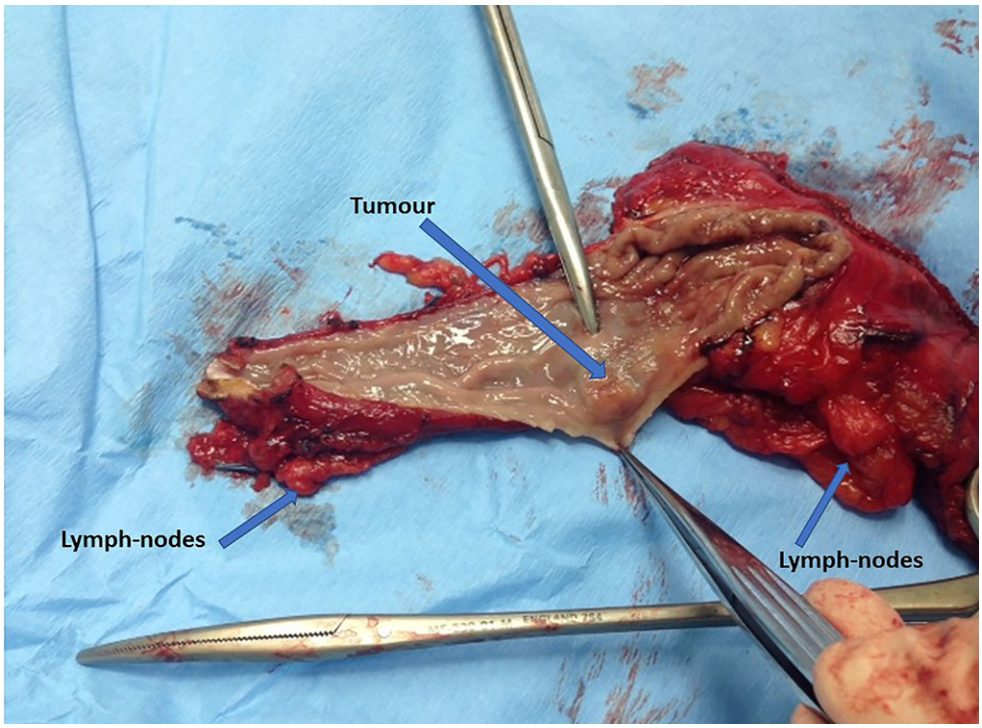


Fig. 5 Oesophageal cancer open surgical view with lymph nodes

malignancy within Barrett's oesophagus, then treatment of the Barrett's is required [35, 36]. A systematic review [37] of 3802 patients treated with radiofrequency ablation found that for dysplasia and metaplasia, complete eradication was achieved in 91% and 78%, respectively. After eradication, intestinal metaplasia recurred in 13%, with progression to cancer in 0.2% during therapy and 0.7% after complete eradication. A 5% oesophageal stricture rate was observed.

Submucosal subclassification in this study demonstrated a high nodal metastasis rate in SM3 (significantly higher than SM1 and SM2). Mucosal invasion is imprecise due to the inability to remove the submucosa in its entirety by EMR and ESD, and therefore it is difficult to accurately assess the level of invasion. The level of invasion in Barrett's oesophagus of 500 µm within the submucosa, corresponding to SM1, has been deemed the cut-off for nodal metastasis [38]. However, at this level we have identified a 17.9% nodal metastasis rate, and because of this, it is our view that most T1b patients should be offered oesophagectomy if medically fit for surgery. However, 500 µm is featured in the current European guidelines for endoscopic resection [39]. Perhaps endoscopic resection has a low nodal malignant incidence with no lymphovascular invasion or poor differentiation in SM1 disease [40, 41]. Generally, resection has been preferred for SM1, SM2 and SM3 submucosal cancers [42].

A recent multicentre study demonstrated that histological high-risk factors were deep submucosal invasion, a tumour greater than 2 cm, presence of lymphovascular invasion and poor differentiation [14]. Ancona et al. [43] found in SM1 and SM2 carcinoma that rates of lymph node metastasis varied negatively with lymphocyte infiltrate and positively with depth of infiltration, lymphovascular invasion and neural invasion. Neural invasion had the greatest accuracy. Endoscopic criteria according to the Paris classification would indicate the rate of lymph node involvement is scarce in type 0–I and 0–II, but increases in excavated ulcerated lesions type 0–III. Noble et al. [3] investigated the accuracy of the Lee and Weksler scores predominantly in T1b patients in an effort to develop a more precise prediction of lymph node status, but found a high false-positive rate. Currently, it would seem that prediction of the status of lymph nodes in early oesophageal carcinoma is somewhat fraught.

Alternatively, oesophagectomy offers both curative and prophylactic treatment of EAC and Barrett's oesophagus. Historically, oesophagectomy was associated with high morbidity and mortality (10%); however, with management shifting to specialised units, as demonstrated by the 2016 AUGIS audit, low mortality (1.9%) and adequate length of stay (12 days) can be achieved. Similarly, in 2014 a literature review [44] including 530 patients a 0.94% mortality was achieved for patients with high-grade dysplasia.

Another study of 100 patients undergoing resection (Fig. 5) for T1 oesophageal cancer demonstrated a 30-day mortality of 0% [45].

Despite excellent improvement in surgical morbidity and mortality, oesophagectomy is still considered a radical approach in the treatment of T1a disease, due to perceived poor postoperative quality of life. Oesophagectomy for EAC is common practice for lesions with T1b disease. As demonstrated by our data,

the risk of lymph node positivity in T1b is high at 22% and, therefore, resection is the preferred option for T1b disease.

Conclusion

There is a moderately high rate of lymph node metastasis in SM1 and SM2 T1 b early oesophageal adenocarcinoma approaching 20%. This factor needs to be taken into consideration when tailoring management in early oesophageal carcinoma. There is a higher rate of lymph node metastasis in SM3 early oesophageal carcinoma precluding endoscopic management. There are other risk factors which can predict lymph node involvement, including morphology of the lesion, neural invasion, lymphovascular invasion and grade of tumour.

Acknowledgements To Suzanna Gooley for editorial assistance.

Conflict of interest D.P. Mitchell, S. Yeluri, H. Van der Wall and G.L. Falk declare that they have no competing interests.

References

Cited Literature

1. Ajani JA, et al. Esophageal and Esophagogastric Junction Cancers, version2.2019, NCCNClinical Practice Guidelines in oncology. J Natl Compr Canc Netw. 2019;17(7):855–883
2. Chadwick G, Varagunam M, Brand C, et al. National Oesophag-Gastric Cancer Audit. An Audit of the care received by people with Oesophago-Gastric Cancer in England and Wales. Ninth Annual Report 2016. L.N.I. Centre; 2016.
3. Nobel T, et al. Ongoing challenges with clinical assessment of nodal status in T1 esophageal adenocarcinoma. J Am Coll Surg. 2018;229(4):366–73.
4. van Hagen P, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074–84.
5. Cunningham D, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11–20.
6. Gockel I, et al. Prediction model of lymph node metastasis in superficial esophageal adenocarcinoma and squamous cell cancer including D2-40 immunostaining. J Surg Oncol. 2009;100(3):191–8.
7. Stein HJ, et al. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. Ann Surg. 2005;242(4):566–73. discussion 573–575.
8. Holscher AH, et al. Prognostic impact of upper, middle, and lower third mucosal or submucosal infiltration in early esophageal cancer. Ann Surg. 2011;254(5):802–7. discussion 807–808.
9. Sepesi B, et al. Are endoscopic therapies appropriate for superficial submucosal esophageal adenocarcinoma? An analysis of esophagectomy specimens. J Am Coll Surg. 2010;210(4):418–27.
10. Nigro JJ, et al. Prevalence and location of nodal metastases in distal esophageal adenocarcinoma confined to the wall: implications for therapy. J Thorac Cardiovasc Surg. 1999;117(1):16–23. discussion 23–25.
11. Griffin SM, Burt AD, Jennings NA. Lymph node metastasis in early esophageal adenocarcinoma. Ann Surg. 2011;254(5):731–6. discussion 736–737.
12. Badreddine RJ, Prasad G, Lewis JT, Lutzke LS, Borkenhagen LS, Dunagan KT, et al. Depth of submucosal invasion does not predict lymph node metastasis and survival of patients with esophageal carcinoma. Clin Gastroenterol Hepatol. 2010;8(3):248–53.
13. Manner H, et al. The frequency of lymph node metastasis in early-stage adenocarcinoma of the esophagus with incipient submucosal invasion (pT1b sm1) depending on histological risk patterns. Surg Endosc. 2015;29(7):1888–96.
14. Leers JM, et al. The prevalence of lymph node metastases in patients with T1 esophageal adenocarcinoma a retrospective review of esophagectomy specimens. Ann Surg. 2011;253(2):271–8.
15. Gertler R, et al. Prevalence and topography of lymph node metastases in early esophageal and gastric cancer. Ann Surg. 2014;259(1):96–101.
16. Lee L, et al. Predicting lymph node metastases in early esophageal adenocarcinoma using a simple scoring system. J Am Coll Surg. 2013;217(2):191–9.
17. Nentwich MF, et al. Depth of submucosal tumor infiltration and its relevance in lymphatic metastasis formation for T1b squamous cell and adenocarcinomas of the esophagus. J Gastrointest Surg. 2014;18(2):242–9. discussion 249.
18. Bogoevski D, et al. How radical should surgery be for early esophageal cancer? World J Surg. 2011;35(6):1311–20.
19. Hagen JA, et al. Curative resection for esophageal adenocarcinoma: analysis of 100 en bloc esophagectomies. Ann Surg. 2001;234(4):520–30. discussion 530–531.
20. Molena D, et al. Esophagectomy following endoscopic resection of submucosal esophageal cancer: a highly curative procedure even with nodal metastases. J Gastrointest Surg. 2017;21(1):62–7.
21. Bollschweiler E, et al. High rate of lymph-node metastasis in submucosal esophageal squamous-cell carcinomas and adenocarcinomas. Endoscopy. 2006;38(2):149–56.
22. Samson P, et al. Adhering to quality measures in esophagectomy is associated with improved survival in all stages of esophageal cancer. Ann Thorac Surg. 2017;103(4):1101–8.
23. Altorki NK, et al. Multifocal neoplasia and nodal metastases in T1 esophageal carcinoma: implications for endoscopic treatment. Ann Surg. 2008;247(3):434–9.
24. Greenstein AJ, et al. Prognostic significance of the number of lymph node metastases in esophageal cancer. J Am Coll Surg. 2008;206(2):239–46.
25. Peyre CG, et al. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg. 2008;248(4):549–56.
26. Rizk NP, et al. Optimum lymphadenectomy for esophageal cancer. Ann Surg. 2010;251(1):46–50.
27. Rösch T. Endosonographic staging of esophageal cancer: a review of literature results. Gastrointest Endosc Clin N Am. 1995;5(3):537–47.
28. Sandha GS, et al. Is positron emission tomography useful in locoregional staging of esophageal cancer? Results of a multidisciplinary initiative comparing CT, positron emission tomography, and EUS. Gastrointest Endosc. 2008;67(3):402–9.
29. Cuellar SL, et al. Clinical staging of patients with early esophageal adenocarcinoma: does FDG-PET/CT have a role? J Thorac Oncol. 2014;9(8):1202–6.
30. van Vliet EP, et al. Staging investigations for oesophageal cancer: a meta-analysis. Br J Cancer. 2008;98(3):547–57.

31. Ell C, et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointest Endosc. 2007;65(1):3–10.
32. Pech O, et al. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. Gastroenterology. 2014;146(3):652–660e1.
33. Manner H, et al. Long-term results of endoscopic resection in early gastric cancer: the Western experience. Am J Gastroenterol. 2009;104(3):566–73.
34. Collard JM. High-grade dysplasia in Barrett's esophagus. The case for esophagectomy. Chest Surg Clin N Am. 2002;12(1):77–92.
35. Van Vilsteren FG, et al. Stepwise radical endoscopic resection versus radiofrequency ablation for Barrett's oesophagus with high-grade dysplasia or early cancer: a multicentre randomised trial. Gut. 2011;60(6):765–73.
36. Phoa KN, et al. Multimodality endoscopic eradication for neoplastic Barrett oesophagus: results of an European multicentre study (EURO-II). Gut. 2016;65(4):555–62.
37. Orman ES, et al. Efficacy and durability of radiofrequency ablation for Barrett's Esophagus: systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013;11(10):1245–55.
38. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach and colon. GastroIntest Endo. 2003;58(6Suppl):S3-43
39. Weusten B, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) position statement. Endoscopy. 2017;49:2589–97.
40. Manner H, et al. Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. Am J Gastroenterol. 2008;103(10):2589–97.
41. Alvarez Herrero L, et al. Risk of lymph node metastasis associated with deeper invasion by early adenocarcinoma of the esophagus and cardia: study based on endoscopic resection specimens. Endoscopy. 2010;42(12):1030–6.
42. Bergman JJ. UPTODATE.COM. 2017. www.uptodate.acs.hcm.com. Accessed: 11 July 2018.
43. Ancona E, et al. Prediction of lymph node status in superficial esophageal carcinoma. Ann Surg Oncol. 2008;15(11):3278–88.
44. Wani S, et al. Comparison of endoscopic therapies and surgical resection in patients with oesophageal cancer: a population-based study. Gastrointest Endosc. 2014;79(2):224–32.
45. Pennathur A, et al. Esophagectomy for T1 esophageal cancer: outcomes in 100 patients and implications for endoscopic therapy. Ann Thorac Surg. 2009;87(4):1048–54. discussion 1054–1055.
46. Rice TW, et al. 8th edition AJCC/UICC staging of cancers of the esophahstric junction: application to clinical practice. Ann Cardiothorac Surg. 2017;6(2):119–30.

Further Reading

47. American Cancer Society. Cancer Facts and Figures. Atlanta: Ga; 2016. Available from: http://www.cancer.org/cancer/esophaguscancer/detailedguide/esophagus-cancer-survival-rates.

World J Surg (2018) 42:1787–1791
https://doi.org/10.1007/s00268-017-4369-9

ORIGINAL SCIENTIFIC REPORT

A Novel Technique of Paravertebral Thoracic and Preperitoneal Analgesia Enhances Early Recovery After Oesophagectomy

Stephanie Phillips[1,2] · Jasmina Dedic-Hagan[1] · d'Arcy Ferris Baxter[3] · H. Van der Wall[4] · G. L. Falk[2,5,6]

Published online: 21 November 2017

Abstract

Background Excellent analgesia following oesophagectomy facilitates patient comfort, early extubation, physiotherapy and mobilisation, reduces post-operative complications and should enhance recovery. Thoracic epidural analgesia (TEA), the gold standard analgesic regimen for this procedure, is often associated with systemic hypotension treated with inotropes or fluid. This may compromise enhanced recovery and be complicated by anastomotic ischaemia or tissue oedema.

Methods We report a novel analgesic regimen to reduce post-operative inotrope usage. Infusion of ropivicaine via bilateral preperitoneal and right paravertebral catheters was used. Patient-controlled epidural pethidine provided rescue analgesia (WC) ($n = 21$). A retrospective audit of inotrope requirement, mean pain scores, episodes of respiratory depression and excessive sedation, need for reintubation, reoperation in the first 5 post-operative days, time to mobilisation, time in intensive care, time in hospital and 30-day mortality were measured. These results were compared with those of an earlier patient group who received a thoracic epidural infusion of low-dose local anaesthetic and fentanyl (TEA) ($n = 21$).

Results Inotrope use was reduced by 29% in the WC group ($p = 0.03$) and the mean intensive care stay reduced by 2.4 days ($p = 0.03$), as was reintubation rate ($p = 0.01$) and early mobilisation ($p = 0.03$). The pain score was comparable in both groups, and there was no difference in the other outcomes examined.

Conclusion The data demonstrated that it was possible to provide excellent post-oesophagectomy analgesia equivalent to thoracic epidural infusions of local anaesthetic with reduction in inotrope requirements, intensive care stay, more rapid mobilisation, facilitating enhanced recovery.

✉ G. L. Falk
sydney.heartburn@gmail.com

Stephanie Phillips
stephanie.phillips@sydney.edu.au

Jasmina Dedic-Hagan
jasmina.hagan@gmail.com

d'Arcy Ferris Baxter
dbax2124@uni.sydney.edu.au

H. Van der Wall
hvanderwall@gmail.com

[1] Sydney Adventist Hospital, Wahroonga, Sydney, Australia

[2] University of Sydney, Sydney, Australia

[3] Sydney Medical School, University of Sydney, Sydney, Australia

[4] Concord Nuclear Imaging, Sydney, Australia

[5] Macquarie University, Sydney, Australia

[6] Suite 29, 12 Tryon Road, Lindfield, NSW 2070, Australia

Introduction

Oesophageal adenocarcinoma has increased in frequency at a rate of 10% per annum for the last 40 years. The current incidence is 4–8 per 100,000 [1]. Modern management involves a multidisciplinary approach, but surgery continues to be required for cure. Mortality can be as high as 8–11%, and morbidity remains as high as 40–50% [2–4]. Provision of excellent post-operative analgesia is a cornerstone of management, facilitating early extubation, chest physiotherapy and mobilisation [4–6], and may be used with other techniques in enhanced recovery pathways with a view to decreased mortality.

Thoracic epidural analgesia (TEA) using low-dose local anaesthetic and opioid mixtures has been the "gold standard" of post-thoracotomy pain control. This technique has also been shown to improve microvascular perfusion of the gastric conduit and is associated with a reduction in anastomotic leak rate [7–10]. However, in our practice, we found TEA produced an unacceptable incidence of hypotension requiring inotropic support. The potential for noradrenaline-induced vasoconstriction compromising the end arterial blood supply to the tip of the gastric conduit has the potential to diminish this effect. This was concerning given a possible fivefold increase in mortality after anastomotic leak [11, 12]. There was also a concern that tachyphylaxis frequently required higher infusion rates leading to leg weakness, comprising mobilisation delaying recovery. Leg weakness could be falsely attributed to the epidural-induced motor block by the nursing staff, when it may in fact be due to a more serious complication. Both leg weakness and inotropes necessitated longer periods in bed.

An alternative analgesic regimen was trialled that aimed to provide adequate analgesia and avoid hypotension, the requirement for inotropes and other potential epidural-related complications. Studies of paravertebral analgesia in thoracotomy alone showed equivalence with TEA, but a decreased side effect profile [10, 13–16]. TEA alone is inadequate for the midline laparotomy frequently required for gastric mobilisation. Bilateral preperitoneal catheter infusion was added. Patient-controlled epidural pethidine (PCEA) as rescue analgesia was provided [17–19].

Results of a comparison of two analgesia regimens, the traditionally used TEA and the newly developed wound catheter infusion (WC), are reported. Data were obtained for inotrope requirement, pain scores, reintubation rates, reoperation rates, length of stay in intensive care, length of hospital stay and 30-day mortality.

Materials and methods

Institutional human ethics and research committee's approval was obtained (EC00141:2011/036), and a retrospective review of records of all two-stage (laparotomy/thoracotomy), two-field lymphadenectomy (Ivor Lewis) oesophagectomy patients in a single-surgeon, single-site private practice from 2000 to 2013 was obtained.

All patients had a thoracic epidural sited before induction of general anaesthesia and used intraoperatively for analgesia. The earlier group (TEA) received a thoracic epidural infusion of low-dose local anaesthetic (either 0.125% bupivicaine or 0.2% ropivicaine with fentanyl 2 μg/ml) post-operatively. The more recent group (WC) received continuous three-site-wound infiltration of 0.2% ropivicaine delivered by fibroelastic devices (on Q^{TM}) into right paravertebral and bilateral preperitoneal catheters all inserted intraoperatively. Each catheter delivered a 5 ml/h infusion with sufficient volume to last 110 hours (total 15 ml/h). Patient-controlled epidural pethidine (5 mg/ml, 20 mg bolus, 20 min lockout, 1 mg/h background) was available as rescue analgesia (PCEA).

Extubation at the conclusion of the surgical procedure was planned for all patients who were then returned to intensive care unit for ongoing management. Regular paracetamol (either intravenous or jejunostomy) and non-steroidal anti-inflammatory medication if not contraindicated was standard. Epidural duration was planned for 5 days. All intensive care management was the domain of the intensive care specialist. Nursing observations, including pain scores (using a 10-cm visual analogue scale), sedation scores (0 = awake, 1 = sleepy, 2 = unrousable) and respiratory rate, were taken hourly for the first 6, 2nd hourly for 24 h and then 4 hourly for 5 post-operative days. Nursing observations during the first 5 post-operative days were audited.

Demographic details collected included age, sex, body mass index (BMI computed from height and weight), American Society of Anaesthesiologists physical status grade (ASA) and operative time in minutes.

The primary outcome measure was any need for inotropic support (noradrenaline infusion) after admission to intensive care and for 5 post-operative days.

Secondary outcome measures were mean daily pain scores, the number of episodes of sedation score = 2, respiratory rate $\leq$8, need for reintubation, reoperation, time to mobilisation (hours), length of ICU stay, length of hospital stay, 30-day mortality and symptomatic anastomotic leakage.

Statistical analysis was performed using Statistica version 10 (StatSoft, Tulsa, USA). Descriptive statistics were utilised for the demographics of the two groups. The means

of the variables of the two groups were tested for significant differences using the independent t test, which was also used to analyse the outcome differences between the groups for inotrope use, pain scores, hours ventilated, ICU stay, days in hospital and 30-day mortality. If variance of the two groups was dissimilar by the Levene test ($p < 0.05$), then outlying or extreme results were symmetrically discarded from each group [20]. Multiple regression analysis was used to analyse the sequential pain scores against other variables such as operative time and method of pain relief. Results were considered significant if $p < 0.05$.

Results

There were 55 cases identified. Alternative analgesic techniques were employed in 13 who were excluded (1 intravenous analgesia only, 4 PCEA only, 8 intrathecal morphine and WC). Three patients in the WC group received fentanyl via PCEA instead of pethidine due to allergy or renal impairment, and one was changed to fentanyl on day 3 due to confusion.

Demographic details of patients were no different in all respects but for height (Table 1). In-hospital mortality occurred in two and anastomotic leak in one (WC group).

Two patients in the WC group were electively ventilated for 12 and 15 h post-operatively due to a combination of obesity and late time of completion of surgery, so data requiring patient cooperation during this time are not available. Removed or dislodged catheters occurred in two (WC), and one (TEA) on day 4; data to this point are included. Acute bowel obstruction occurred in the TEA group [1] and was returned to theatre on post-operative day 3 and subsequently died on day 24. Data until return to theatre are included.

There were significantly fewer patients requiring noradrenaline infusion in the WC arm for analgesia-related hypotension, and 2 had inotropes for management of haemorrhage (Table 2). There were fewer patients requiring reintubation or reoperation in the first 5 post-operative days in the WC group as was the time to mobilisation. The length of hospital stay was substantially decreased in the WC arm, but the difference was not statistically significant (Table 2). The mean daily pain scores were similar in both groups (Table 3).

There were six episodes of respiratory depression in the TEA group and one in the WC group. This was significantly better in the WC group ($p = 0.016$). There was one episode of excessive sedation in each group. No patient experienced any neurological complications. No incidence of infection related to the epidural catheter or pain catheters was identified.

Anastomotic leak occurred in one patient in the WC group, who received inotropes. Hospital stay was 143 days. As an extreme statistical outlier, this was excluded from the mean hospital stay calculation.

Discussion

This series demonstrates that it is possible to provide clinically acceptable equivalent analgesia after Ivor Lewis oesophagectomy without using epidural infusion. A reduction in the need for inotrope infusions was evident. The reduction in time in intensive care in the WC group by a mean of 2.4 days was both clinically and statistically significant and may have related to the reduced requirement for arterial pressure support. However, this series is congruent with others utilising similar techniques [10, 13, 16, 19, 21] for single-incision surgery. The total hourly dose of ropivicaine was similar in both groups, but the use of fibroelastic WC devices required minimal supervision and had potential to reduce nursing workload. Although the benefits of a reduction in the need for inotrope use were not assessable from this study, patient outcomes were at least as good as those of historical controls. It was our clinical experience that the requirement for inotropes reduced mobilisation and WC routinely enabled walking on day 1 in ICU. Both findings were significantly improved upon the TEA group.

During the commencement of the new analgesic regimen, it was necessary to ensure the availability of acceptable rescue analgesia. This was especially so in a procedure where successful outcomes are analgesia dependent. TEA was placed in all patients, providing an option to easily institute TEA should the novel technique deliver inadequate analgesia.

The recent post hoc analysis of the POISE trial showed that patients at high risk of cardiovascular morbidity undergoing TEA combined with general anaesthesia were at a threefold increased risk of serious cardiovascular complications [22]. Using the definitions of the POISE investigators, many of our patients might be classified in this group (intrathoracic + intraperitoneal procedure, age > 70, history of coronary heart disease or peripheral vascular disease). Clinically significant hypotension, a known cause of post-operative morbidity, may lead to an increased risk of mortality and myocardial infarction. Effective multimodal analgesic regimens without the need for TEA may reduce this potential.

It has become increasingly accepted that principles of enhanced recovery can lead to improved outcome [6, 23, 24]. The standardised management of the cases reported herein may have influenced this outcome. There is little doubt that the WC approach enabled early

Table 1 Demographic data (mean ± SD except sex—*n* (%))

	TEA $n = 21$	WC $n = 21$	*p*
Age (years)	63.9 ± 9.0	63.3 ± 7.8	NS
Male sex	14 (67)	19 (86)	NS
BMI	26.33 ± 4.45	28.0 ± 5.80	NS
ASA physical status	2.3 ± 0.6	2.1 ± 0.4	NS
Length of surgery (hours)	4.47 ± 0.38	6.1 ± 0.23	NS
Height (meters)	1.7 ± 0.07	1.8 ± 0.08	0.00

TEA thoracic epidural analgesia, *WC* bilateral peritoneal wound and right paravertebral infusions + patient-controlled epidural pethidine, *BMI* Body Mass Index, *ASA* American Society of Anaesthesiologists, *NS* not significant

Table 2 Primary and secondary outcomes (*n* or mean ± SD)

	TEA $n = 21$	WC $n = 21$	*p*
Inotrope use (%)	13 (62)	7 (33)	0.03
Episodes of sedation score ≥2	1	1	NS
Episodes of respiratory depression	6	2	NS
Reintubated	3	1	0.013
Reoperation	2	2	NS
Hours to mobilisation	28.3	22.7	0.03
Days in ICU	6.0	3.6	0.03
Days in hospital	23.5 ± 4.8	16.5 ± 2.0	NS
30-day mortality	2	0	NS

A total of 756 observations were taken per study group during the first 5 post-op days

TEA thoracic epidural analgesia, *WC* bilateral peritoneal wound and right paravertebral infusions + patient-controlled epidural analgesia

Table 3 Daily pain scores (mean ± SD)

Post-op day	TEA $n = 21$	WC $n = 21$
1	1.9 ± 1.7	1.2 ± 0.9
2	1.2 ± 1.2	1.3 ± 1.4
3	0.8 ± 0.9	1.1 ± 1.1
4	0.7 ± 0.9	1.2 ± 1.2
5	0.9 ± 0.9	1.3 ± 1.8

TEA thoracic epidural analgesia, *WC* bilateral peritoneal wound and right paravertebral infusions + patient-controlled epidural pethidine

mobilisation due to good pain relief and lack of morbidity from TEA. A decrease in average hospital stay of 1 week was seen, suggesting a substantial yet statistically insignificant effect. There are potential benefits of avoiding TEA such as a reduction in intravenous fluid therapy, leg weakness and other hypotension-related potential morbidity. Atrial fibrillation, pulmonary collapse, blood transfusion requirements, post-thoracotomy pain and venous thromboembolism were not evaluated.

The confidence of difference in outcome seen is limited by the small sample size and retrospective nature of the study. Outcome may have been influenced by the use of the harmonic scalpel, haemostatic technique, avoidance of transfusion, more restrictive and goal-directed fluid therapy, the introduction of ropivicaine, gabapentin and patient warming devices. The surgical team, however, was consistent, and the post-operative management of the entire series was protocol driven and unchanged between time periods and patient cohorts.

The time taken for a single practice to accumulate cases in such a specialised area makes accumulation of adequate numbers for prospective randomised trials unlikely in a timely fashion. Long data acquisition periods may see changes in clinical practice which could prevent compliance with the study protocol [4, 5]. Larger units may be able to compare techniques in a random and timely fashion. Prospective audit of changes to practice, however, remains important if outcomes are to be objectively maintained and improved, and the results herein attest the efficacy of this technique.

Conclusion

Pain control with the use of wound catheter analgesia in two-stage radical lymphadenectomy oesophagectomy is equivalent to pain control with thoracic epidural, reduces inotrope requirements and ICU stay and has the potential to enhance recovery.

Compliance with ethical standards

Conflict of interest There were no conflicts of interest.

Ethical approval All ethical requirements were met.

References

1. Hongo M, Nagasaki Y, Shoji T (2009) Epidemiology of esophageal cancer: orient to occident. Effects of chronology, geography and ethnicity. J Gastroenterol Hepatol 24(5):729–735
2. Chandrashekar MV, Irving M, Wayman J et al (2003) Immediate extubation and epidural analgesia allow safe management in a high-dependency unit after two-stage oesophagectomy. Results of eight years of experience in a specialized upper gastrointestinal unit in a district general hospital. Br J Anaesth 90(4):474–479
3. Chang AC, Ji H, Birkmeyer NJ, Orringer MB et al (2008) Outcomes after transhiatal and transthoracic esophagectomy for cancer. Ann Thorac Surg 85(2):424–429
4. Ng J-M (2011) Update on anesthetic management for esophagectomy. Curr Opin Anaesthesiol 24(1):37–43
5. Jaeger JM, Collins SR, Blank RS (2012) Anesthetic management for esophageal resection. Anesthesiol Clin 30(4):731–747
6. Preston SR, Markar SR, Baker CR et al (2013) Impact of a multidisciplinary standardized clinical pathway on perioperative outcomes in patients with oesophageal cancer. Br J Surg 100(1):105–112
7. Ali M, Winter DC, Hanly AM et al (2010) Prospective, randomized, controlled trial of thoracic epidural or patient-controlled opiate analgesia on perioperative quality of life. Br J Anaesth 104(3):292–297
8. Rigg JRA, Jamrozik K, Myles PS et al (2002) Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. Lancet 359(9314):1276–1282
9. Flisberg P, Törnebrandt K, Walther B et al (2001) Pain relief after esophagectomy: thoracic epidural analgesia is better than parenteral opioids. J Cardiothorac Vasc Anesth 15(3):282–287
10. Wenk M, Schug SA (2011) Perioperative pain management after thoracotomy. Curr Opin Anaesthesiol. 24(1):8–12
11. Al-Rawi OY, Pennefather SH, Page RD et al (2008) The effect of thoracic epidural bupivacaine and an intravenous adrenaline infusion on gastric tube blood flow during esophagectomy. Anesth Analg 106(3):884–887
12. Freise H, Van Aken HK (2011) Risks and benefits of thoracic epidural anaesthesia. Br J Anaesth 107(6):859–868
13. Joshi GP, Bonnet F, Shah R et al (2008) A systematic review of randomized trials evaluating regional techniques for postthoracotomy analgesia. Anesth Analg 107(3):1026–1040
14. Dango S, Harris S, Offner K et al (2013) Combined paravertebral and intrathecal vs thoracic epidural analgesia for post-thoracotomy pain relief. Br J Anaesth 110(3):443–449
15. Wheatley GH, Rosenbaum DH, Paul MC et al (2005) Improved pain management outcomes with continuous infusion of a local anesthetic after thoracotomy. J Thorac Cardiovasc Surg 130(2):464–468
16. Davies RG, Myles PS, Graham JM (2006) A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy—a systematic review and meta-analysis of randomized trials. Br J Anaesth 96(4):418–426
17. Beaussier M, El'Ayoubi H, Schiffer E et al (2007) Continuous preperitoneal infusion of ropivacaine provides effective analgesia and accelerates recovery after colorectal surgery: a randomized, double-blind, placebo-controlled study. Anesthesiology 107(3):461–468
18. Bertoglio S, Fabiani F, De Negri P et al (2012) The postoperative analgesic efficacy of preperitoneal continuous wound infusion compared to epidural continuous infusion with local anesthetics after colorectal cancer surgery: a randomized controlled multicenter study. Anesth Analg 115(6):1442–1450
19. Liu SS, Richman JM, Thirlby RC et al (2006) Efficacy of continuous wound catheters delivering local anesthetic for postoperative analgesia: a quantitative and qualitative systematic review of randomized controlled trials. J Am Coll Surg 203(6):914–932
20. Levene H (1960) Robust test for equality of variance. In: Okin H (ed) Contributions to probability and statistics: essays in honor of harold hotelling. Stanford University Press, Palo Alto, pp 278–292
21. Mann V, Mann S, Hecker A et al (2011) Continuous local wound infusion with local anesthetics. Der Chir 82(10):906–912
22. Leslie K, Myles P, Devereaux P et al (2013) Neuraxial block, death and serious cardiovascular morbidity in the POISE trial. Br J Anaesth 111(3):382–390
23. Low DE, Kunz S, Schembre D et al (2007) Esophagectomy-it's not just about mortality anymore: Standardized perioperative clinical pathways improve outcomes in patients with esophageal cancer. J Gastrointest Surg 11(11):1395–1402
24. Tomaszek SC, Cassivi SD, Allen MS et al (2010) An alternative postoperative pathway reduces length of hospitalisation following oesophagectomy. Eur J Cardio Thorac Surg 37(4):807–813

International Journal of Surgery Case Reports 23 (2016) 12–16

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

Chlyous leak after radical oesophagectomy: Thoracic duct lymphangiography and embolisation (TDE)—A case report

M. Atie[a,*], G. Dunn[b], G.L. Falk[a]

[a] Department of Upper GI Surgery, Concord Repatriation General Hospital, Hospital Road, Sydney, NSW 2139, Australia
[b] Department of Radiology, Concord Repatriation General Hospital, Hospital Road, Sydney, NSW 2139, Australia

ARTICLE INFO

Article history:
Received 27 January 2016
Received in revised form 17 March 2016
Accepted 2 April 2016
Available online 7 April 2016

ABSTRACT

INTRODUCTION: Chyle leak after oesophagectomy is highly morbid and may carry significant mortality if treatment is delayed. Identification of the site of leakage and surgery may be plagued by failure.
PRESENTATION OF CASE: We describe a case of chyle leak after oesophagectomy. Lymphangiography revealed the site of chyle leak to be an aberrant duct that would have been difficult to identify surgically. Radiological coiling and embolization successfully treated the leak.
DISCUSSION: The gold standard for treatment of chyle leak or chylothorax after oesophagectomy was a re-operation, either open or thoracoscopic, to ligate the thoracic duct. The interventional radiological technique employed in our case was not only efficacious in stopping the leak, but had the added advantage of identifying the site and highlighting the anatomy hence avoiding a morbid reoperation. The literature is reviewed.
CONCLUSION: The report and review confirm that lymphangiography followed by coiling and embolization for chylothorax post oesophagectomy is safe and effective in a majority of cases.

1. Introduction

Thoracic duct anatomy must be understood in the context of its embryology. The first lymph sacs to develop in the human body are the paired jugular lymph sacs at the junction of the internal jugular and subclavian veins. The jugular lymph sacs communicate inferiorly with the cisterna chyli. Channels that join the jugular lymph sacs to the cisterna chyli become the thoracic duct (left lymphatic duct) and the right lymphatic duct. Disturbances in processes that govern the formation of these lymphatic channels can result in anatomical variations of the thoracic duct [1–3].

The thoracic duct is a tubular structure that is 2–3 mm in diameter and varies in length from 38 to 45 cm. It begins in the abdomen at the level of the second lumbar vertebra. It enters the thorax through the aortic opening of the diaphragm between the aorta and the azygous vein. The thoracic duct then passes cephalad on the right side of the aorta and crosses to the left side at the level of the fifth cervical vertebra where it joins the venous system. The previously described course of the thoracic duct has an incidence of 60–65%. The thoracic duct may also be partially duplicated in 15–20% of the time or fully duplicated in 15%. These anatomical variations provide a reason why the thoracic duct gets damaged during surgery despite the surgeon's vigilance [3–5].

The complication rate of oesophageal surgery is relatively high, in the region of 30–40%. The thoracic duct can often be damaged during mobilisation of advanced oesophageal cancers, whether via a right thoracotomy or through the *trans*-hiatal route. A comprehensive review reports chylothorax occurring in up to 10% of patients after blunt *trans*-hiatal oesophagectomy [6]. An incidence of 2–3%, during open trans-thoracic resection, is commonly reported [7].

In the event of thoracic duct injury, chylothorax usually presents in the first 7 days after surgery, when the patient has commenced oral intake, or jejunostomy feeds. A massive increase in chest drainage occurs that if left untreated, results in malnutrition and significant immune suppression, with a markedly reduced CD4 count from the subsequent white cell loss [8].

Leaks of less than 500 mL/day may resolve with enteral feeding using medium-chain triglyceride. Octreotide/somatostatin and etilefrine therapy may also be highly efficacious in the conservative management of low volume chylothorax. High volume leaks, however, warrant immediate re-exploration as the damaged thoracic duct is usually easily identified, following a bolus of "cream" at the time of re-exploration [7]. Open or thoracoscopic exploration had been established as the gold standard of treatment.

We describe a case of chyle leak post radical 2- stage oesophagectomy (Ivor-Lewis) with two-field lymph node dissection. The gold standard of treatment that we grew accustomed

* Corresponding author.
E-mail addresses: moatiemd@yahoo.com (M. Atie), dunng@email.cs.nsw.gov.au (G. Dunn), sydney.heartburn@gmail.com (G.L. Falk).

http://dx.doi.org/10.1016/j.ijscr.2016.04.002

to was not employed in the management of our case but rather lymphangiography was used to identify the anatomy and the site of the leak. The leak was then successfully treated by means of radiological coiling and embolization.

2. Case report

A 69-year-old male presented with dysphagia to solids and vomiting. Weight loss was denied, and appetite was good. Past medical history was significant for hypercholestrolaemia, diverticular disease, renal calculi, parathyroidectomy for hyperparathyroidism and benign prostatic hypertrophy.

Endoscopy revealed a Seiwert I type junctional/distal oesophageal cancer. Biopsies confirmed adenocarcinoma. Radiology including CT, EUS and PET staged this tumour at T3N0M0. The cancer multidisciplinary meeting consensus was that the criteria for "Magic Protocol" were met.

Treatment with 3 cycles of ECF was followed by radical subtotal oesophagectomy (Ivor-Lewis) with two-field lymph node dissection. A feeding jejunostomy was fashioned during the abdominal stage as is routine in our practice. The thoracic duct was excised during the chest stage of the operation. An apical, basal and mediastinal chest tubes were inserted for drainage. Thoracic and abdominal "pain buster" catheters were positioned intra-operatively for analgesia.

The patient was managed according to our enhanced recovery program. He was mobilized out of bed on the evening of surgery. Vivonex (Nestle Health Science, U.S.A), low fat jejunostomy feeding, was commenced at a rate of 25 mls/hour on day 1 post surgery and was increased by 25 mls every 24 h to a maximum of 75 mls/hour on day 3 post surgery. The output in the chest drains combined averaged less than 200 mls/day on day 3. There was minimal output in the apical drain and therefore it was removed. The basal and mediastinal drains were left in place until a time when radiological assessment of the anastomosis was feasible. Contrast swallow on day 5 confirmed anastomotic integrity and demonstrated good gastric emptying. Apical and basal chest drains were removed by day five, as there was minimal drainage. Chest X-rays showed clear lung fields bilaterally.

Acute respiratory failure developed on day 8 post operatively. The patient was re-admitted to the intensive care unit. Investigations including CT pulmonary angiogram demonstrated the presence of a large effusion on the left side, almost obliterating the entire pleural space (Fig. 1a and b). The right pleural space was unremarkable. All other pathology was excluded. Ultrasound guided drainage of the left pleural effusion revealed that it was chylous in nature. A pigtail drain was inserted in the left chest cavity and a trial of conservative therapy was commenced. Jejunostomy feeds were ceased. Total paraenteral nutrition was commenced. Pantoprazole 40 mgs IV twice daily and Octreotide 200 units SC three times daily were given to slow down gut function.

It is our experience that when a major chyle leak ensues as a result of thoracic duct damage, the volume produced is usually high from the onset. What was intriguing in this case report was the delayed onset of the chyle leak despite having commenced jejunostomy feeding from day 1 post operatively.

Unfortunately, a 5-day trial of conservative therapy was fraught with failure. At almost 2 weeks since surgery, it was felt that the condition of the tissues in the thorax at that point of time would not favour surgical intervention. A radiological approach was therefore sought.

Percutaneous thoracic duct embolization was arranged. Technique: a 25-gauge needle was introduced into the largest right superficial inguinal lymph node under ultrasound guidance. Lipiodol was injected to opacify the lymphatic system up to the cysterna chyli, which was at the level of T12/L1 disc (Fig. 2a). The cysterna chyli was then punctured with a 22-gauge needle and a V18 guidewire (Boston Scientific, U.S.A) was introduced. The latter was exchanged for a Renegade microcatheter (Boston Scientific,U.S.A), which was used to perform a lymphangiogram with the water-soluble contrast medium ioversol 370 flushed with 5% dextrose (anticipating the use of cyanoacrylate which sets in the presence of ionic solutions). The lymphangiograms showed the presence of an aberrant thoracic duct running to the left of the thoracic vertebral column. There was extravasation of contrast medium at the level of T9 (Fig. 2b). A small channel draining towards the right main duct was also seen. The main duct did not opacify consistent with surgical obliterated. Three Tornado coils 50 mm in length and 0.018 in. in diameter (Cook Medical, U.S.A) were deployed in the aberrant duct near the region of extravasation. This was followed by injection of 1 ml of cyanoacrylate (Histoacryl by Braun, Germany) mixed with Lipiodol ultra fluid (Guerbet, France). A repeat lymphangiogram confirmed the absence of further extravasation (Fig. 2c)

Flow from the left pleural drain slowed and drainage had almost ceased by day 2 after the procedure. No pleural fluid was visible on a radiograph of the chest nine days after the lymphangiogram and embolization. The patient's diet was upgraded and he was discharged day 5 post procedure (13 days post-operation).

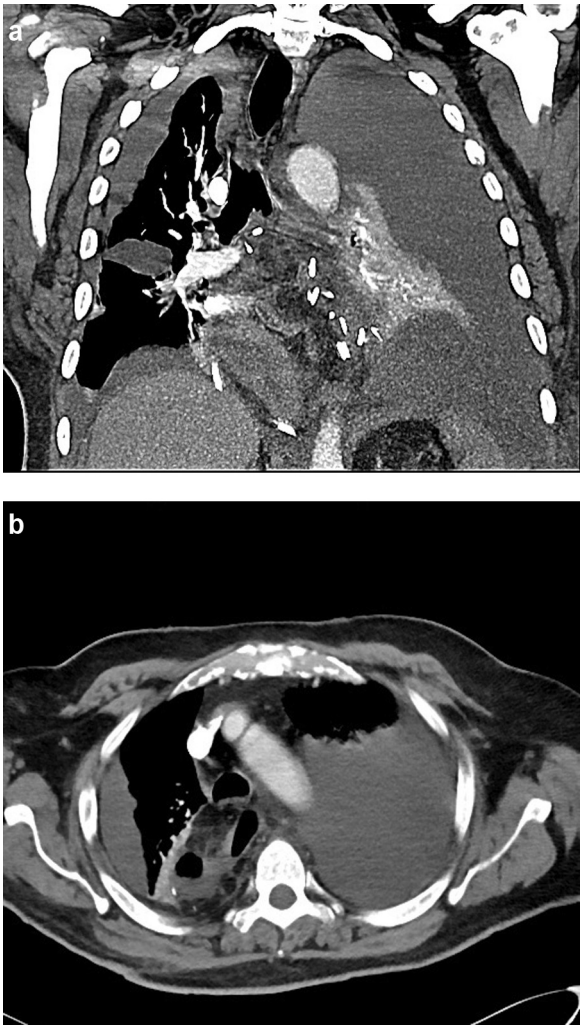


Fig. 1. (a) and (b) coronal and transverse views: "white out" resulting from a large left pleural effusion.

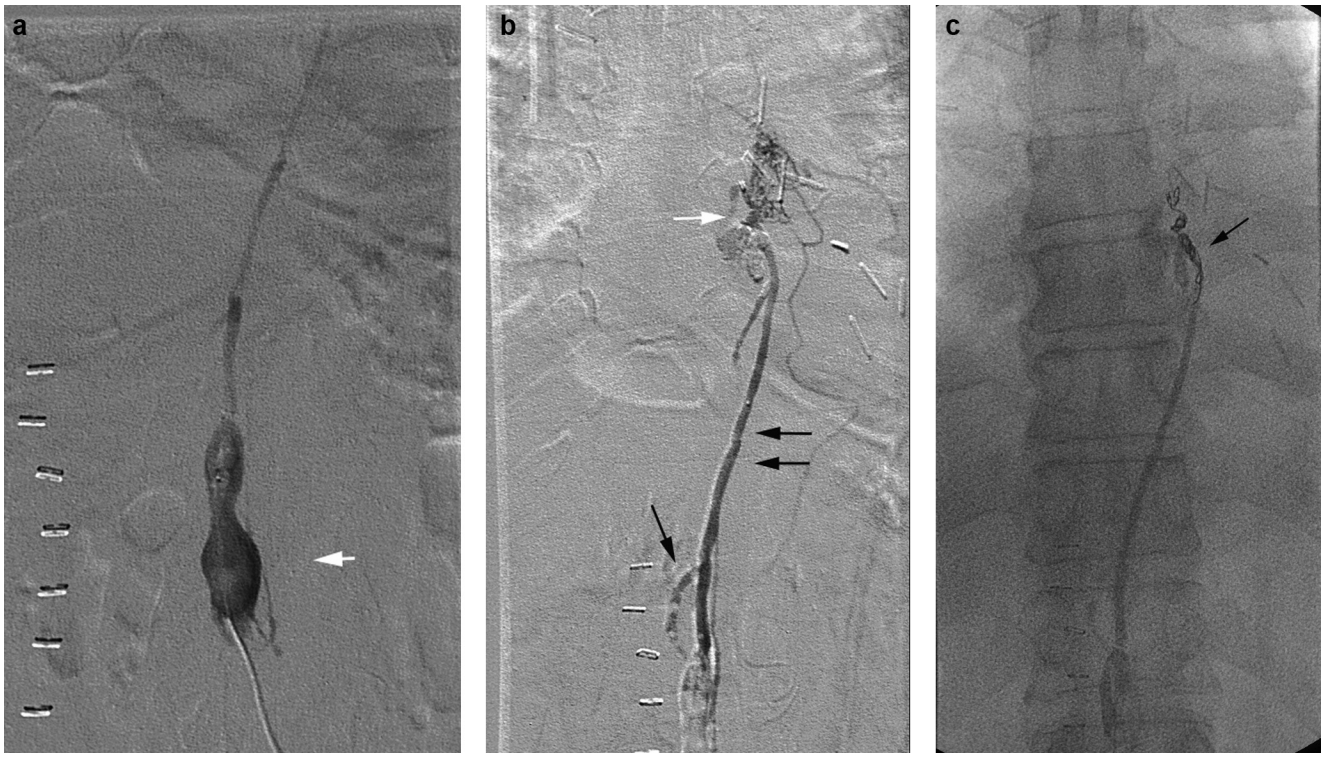


Fig. 2. (a) Lymphangiogram: Lipoiodol injected into superficial inguinal node fills cysterna chyli (white arrow). (b) Lymphangiogram: Aberrant left thoracic duct (2 black arrows) extravasation at T9 (white arrow). A single black arrow points towards a side branch of the thoracic duct. (c) Lymphangiogram: Occlusion of leak following coiling and embolization (black arrow). The side branch has also been occluded.

3. Discussion

Chylothorax after oesophagectomy should be suspected when there is an unexplained high-volume chest tube output which could appear milky after enteral tube feeding is commenced. The exact diagnosis of chylothorax is based on the presence of chylomicrons in the pleural fluid. Chylomicrons are molecular complexes of proteins and lipids that are synthesised in the jejunum and transported via the thoracic duct to the circulation. They are only found in the circulation post-prandially with a peak 3 h after eating [9]. Cytological analysis of fluid stained with Sudan III will demonstrate chylomicrons, which although sensitive, is not specific and therefore should be combined with complementary fluid analysis. In centres with available facilities, lipoprotein analysis demonstrating chylomicrons is the gold standard. Where this facility is not available, institutions rely on the measurement of fluid cholesterol and triglyceride levels. A pleural fluid triglyceride levels >1.24 mmol/l (110 mg/dl) with a cholesterol <5.18 mmol/l (200 mg/dl) is diagnostic of chylothorax [5]

Alexiou et al. [10] carried out a retrospective analysis of 523 patients with cancer of the oesophagus or the gastro-oesophageal junction who underwent oesophageal resection between January 1987 and November 1997. Chylothorax occurred in 21 patients (4.0%). Radicality of dissection was the only apparent predisposing factor.

The management of early post-operative chylothorax requires rigorous scrutiny. The aetiology of the chylothorax, the flow rate and patient condition dictate the preferred management. Interventions are only required if unresponsive to medical management.

Surgical therapy is recommended in cases where despite conservative management, the patient drains more than 1.5/day in an adult or >100 ml/kg body weight per day in a child [11], leaks chyle at a rate of >1 l/day × 5 days [8] or has persistent chyle flow for more than 2 weeks [12]. Surgery is also recommended if there has been a rapid decline in nutritional or immunological status despite conservative management [13–15]. Chylothorax following oesophageal surgery managed with re-exploration is associated with a mortality of 10% compared to a mortality of 50% if managed conservatively [16,17].

Patients with iatrogenic chylothorax after oesophagectomy who are good surgical candidates and in whom the site of the leak is identified, do well following surgical re-exploration. When re-operation is not delayed and simple duct closure of any type is performed, patients have little added morbidity and the reported success rates are around 90% [18]. Ligation of the thoracic duct via a thoracotomy has been considered to be the gold standard approach. Video-assisted thoracic surgery and ligation of the duct has also proven to be a safe and effective approach [19].

Ligation of the thoracic duct is successful in 90% of patients when performed just above the right hemi-diaphragm [20]. Ligating at that site has the advantage of halting flow from any unidentified accessory ducts [21,22]. Collateral circulation re-directs the chyle around the ligation point ensuring that the chyle still completes its journey to the circulation. If the leak is in the region of the neck or upper thorax, the thoracic duct is ligated in the area known as Poirier's triangle between the arch of the aorta, internal carotid and vertebral column [23].

In thoracoscopic ligation, up to 3 ports are inserted strategically between different ribs and the thoracic duct is sought. A short segment of the duct is excised before clipping the remaining ends [13].

If the leak is not identifiable on either thoracoscopy or thoracotomy, then mass ligation of all the tissue between aorta, spine, oesophagus and pericardium is performed [13]. Extensive dissection to find the duct is discouraged reducing the risk of further trauma and leak. Pleurectomy or pleurodesis with talc or glue have been described as alternative options [24]. In cases of loculated or complicated chylothorax, pleural decortication with pleurodesis may be performed [13]. In patients that are unfit for major surgery,

a pleuroperitoneal shunt may be useful. It minimises the nutritional or immunological deficits seen in chylothorax [20].

The accumulation of experience in treating chylous effusions has significantly broadened the adoption of thoracic duct embolization to treat chylothorax. A cannulation and embolisation technique used by Cope et al. [25] to treat chylothorax was curative in patients with demonstratable duct leakage. However, reproducibility and success rates have varied in different centres. More recently Boffa et al. [26] have used the technique of thoracic duct embolisation or disruption with very good effect in patients with chyle leak post thoracic surgery and Litherland et al. [27] described a case report where CT guided disruption of the lymphatics had good effect in the management of high output chylothorax.

Matsumoto et al., performed lymphangiography on 9 patients that were unlikely to respond to conservative measures. They found that lymphangiography not only identified the site of the leak but also led to the leak resolving in all cases. They recommend early lymphangiography in cases unlikely to be cured by conservative methods only [28].

The feasibility and effectiveness of percutaneous thoracic duct embolization or interruption have been reported in four papers.

Marcon et al. [29] reviewed the existing literature on percutaneous management of chyle leaks. The authors evaluated five case series and three case reports inclusive of 90 patients in whom percutaneous treatment for chylothorax was attempted between 1998 and 2004. Percutaneous treatment resulting in successful resolution of the chylothorax was achieved in 69% of the patients. The authors concluded that such percutaneous management of chyle leaks is feasible, with low morbidity and mortality rates and a high rate of effectiveness.

A retrospective review of 34 patients was similarly conducted by Nadolski et al. [30] to assess the technical and clinical success of thoracic duct embolization for iatrogenic chylous effusions. Thoracic duct embolization was technically successful in 24 of 34 patients (70.6%).

A retrospective review of 109 patients was conducted by Itkin et al. [31] to assess the efficacy of thoracic duct embolization or interruption for the treatment of high-output chyle leak caused by injury to the thoracic duct. The authors concluded that catheter embolization or needle interruption of the thoracic duct is safe, feasible, and successful in eliminating a high-output chyle leak in the majority (71%) of patients. Further more, the authors stated that this minimally invasive procedure, although technically challenging, should be the initial approach for the treatment of a traumatic chylothorax.

Pamarthi et al. [32] retrospectively report the indications, technical approach, and clinical outcomes of thoracic duct embolization and thoracic duct disruption in 105 patients with symptomatic chylous effusions. The technical success rate was 79% in this series. The authors concluded that thoracic duct embolization and thoracic duct disruption are safe and effective minimally invasive treatments for traumatic thoracic duct injuries.

4. Conclusion

TDE in this case was technically satisfactory. Chyle leak may occur from aberrant sites as in this case and lymphangiograohy is helpful. High volume chyle leak requires prompt management before immune compromise occurs. TDE is successful in a majority of cases (61–71%) and so should be utilised in reserving surgery for failed percutaneous management.

Conflict of interest

There is no conflict of interest.

Funding

There was no external funding, there were external sponsors.

Ethical approval

This was purely an observational case study. The patient's management and outcome were unaltered. There was no research that involved the patient.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

All of the authors have participated in caring for the patient, preparing and designing the intervention under review, acquiring the data, analysing and interpreting the data, drafting the article, revising it critically for important intellectual content and approving the final version to be submitted.

Guarantor

Professor Greg L. Falk.

Disclosure

All of the authors have participated in caring for the patient, preparing and designing the intervention under review, acquiring the data, analysing and interpreting the data, drafting the article, revising it critically for important intellectual content and approving the final version to be submitted.

References

[1] V. Krutsiak, L. Polianskii, Development of the thoracic duct in the prenatal period of human ontogeny, Arkh. Anat. Gistol. Embriol. 85 (11) (1983) 79–84.
[2] J.F. Neas, et al., The lymphatic system, in: F.H. Martini, M.J. Timmons, B. Tallitsch (Eds.), Human Anatomy, 4th ed., Pearson Education/Benjamin Cummings, Old Teppan: New Jersy, 2003, Chapter 23.
[3] H. Davis, A statistical study of the thoracic duct in man, Am. J. Anat. 17 (2005) 211–244.
[4] J.E. Medina, Neck dissection, in: B.J. Bailey, J.T. Johnson (Eds.), Head and Neck Surgery: Otolaryngology, 2, 4th ed., Lippincott Williams and Wilkins, Philadelphia, Pa, 2006, pp. 1585–1609, Chapter 113.
[5] R.J. Cerfolio, et al., Postoperative chylothorax, J. Thorac. Cardiovasc. Surg. 112 (5) (1996) 1361–1365, discussion 1365-6.
[6] S.A. Wemyss-Holden, B. Launois, G.J. Maddern, Management of thoracic duct injuries after oesophagectomy, Br. J. Surg. 88 (11) (2001) 1442–1448.
[7] S. Merigliano, et al., Chylothorax complicating esophagectomy for cancer: a plea for early thoracic duct ligation, J. Thorac. Cardiovasc. Surg. 119 (3) (2000) 453–457.
[8] L. Dugue, et al., Output of chyle as an indicator of treatment for chylothorax complicating oesophagectomy, Br. J. Surg. 85 (8) (1998) 1147–1149.
[9] H.G. de Beer, M.J. Mol, J.P. Janssen, Chylothorax, Neth. J. Med. 56 (1) (2000) 25–31.
[10] C. Alexiou, et al., Chylothorax following oesophagogastrectomy for malignant disease, Eur. J. Cardiothorac. Surg. 14 (5) (1998) 460–466.
[11] B.C. Marts, et al., Conservative versus surgical management of chylothorax, Am. J. Surg. 164 (5) (1992) 532–534, discussion 534-5.
[12] J.G. Selle, W.H. Snyder 3rd, J.T. Schreiber, Chylothorax: indications for surgery, Ann. Surg. 177 (2) (1973) 245–249.
[13] S.K. Nair, M. Petko, M.P. Hayward, Aetiology and management of chylothorax in adults, Eur. J. Cardiothorac. Surg. 32 (2) (2007) 362–369.
[14] E.M. Sieczka, J.C. Harvey, Early thoracic duct ligation for postoperative chylothorax, J. Surg. Oncol. 61 (1) (1996) 56–60.
[15] J.P. Janssen, H.J. Joosten, P.E. Postmus, Thoracoscopic treatment of postoperative chylothorax after coronary bypass surgery, Thorax 49 (12) (1994) 1273.

[16] C. Bolger, et al., Chylothorax after oesophagectomy, Br. J. Surg. 78 (5) (1991) 587–588.
[17] M.B. Orringer, M. Bluett, G.M. Deeb, Aggressive treatment of chylothorax complicating transhiatal esophagectomy without thoracotomy, Surgery 104 (4) (1988) 720–726.
[18] G. Nadolski, M. Itkin, Thoracic duct embolization for the management of chylothoraces, Curr. Opin. Pulm. Med. 19 (4) (2013) 380–386.
[19] B.J. Slater, S.S. Rothenberg, Thoracoscopic thoracic duct ligation for congenital and acquired disease, J. Laparoendosc. Adv. Surg. Technol. A 25 (7) (2015) 605–657.
[20] M.L. Paes, H. Powell, Chylothorax: an update, Br. J. Hosp. Med. 51 (9) (1994) 482–490.
[21] G.A. Patterson, et al., Supradiaphragmatic ligation of the thoracic duct in intractable chylous fistula, Ann. Thorac. Surg. 32 (1) (1981) 44–49.
[22] H.et al. Miyamura, Ligation of the thoracic duct through transabdominal phrenotomy for chylothorax after heart operations, J. Thorac. Cardiovasc. Surg. 107 (1) (1994) 316.
[23] B.A. Merrigan, D.C. Winter, G.C. O'Sullivan, Chylothorax. Br. J. Surg. 84 (1) (1997) 15–20.
[24] N.L. Browse, D.R. Allen, N.M. Wilson, Management of chylothorax, Br. J. Surg. 84 (12) (1997) 1711–1716.
[25] C. Cope, R. Salem, L.R. Kaiser, Management of chylothorax by percutaneous catheterization and embolization of the thoracic duct: prospective trial, J. Vasc. Interv. Radiol. 10 (9) (1999) 1248–1254.
[26] D.J. Boffa, et al., A critical evaluation of a percutaneous diagnostic and treatment strategy for chylothorax after thoracic surgery, Eur. J. Cardiothorac. Surg. 33 (3) (2008) 435–439.
[27] B. Litherland, M. Given, S. Lyon, Percutaneous radiological management of high-output chylothorax with CT-guided needle disruption, J. Med. Imaging Radiat. Oncol. 52 (2) (2008) 164–167.
[28] T. Matsumoto, et al., The effectiveness of lymphangiography as a treatment method for various chyle leakages, Br. J. Radiol. 82 (976) (2009) 286–290.
[29] F. Marcon, et al., Percutaneous treatment of thoracic duct injuries, Surg. Endosc. 25 (9) (2011) 2844–2848.
[30] G.J. Nadolski, M. Itkin, Thoracic duct embolization for nontraumatic chylous effusion: experience in 34 patients, Chest 143 (1) (2013) 158–163.
[31] M. Itkin, et al., Nonoperative thoracic duct embolization for traumatic thoracic duct leak: experience in 109 patients, J. Thorac. Cardiovasc. Surg. 139 (3) (2010) 584–589, discussion 589-90.
[32] V. Pamarthi, et al., Thoracic duct embolization and disruption for treatment of chylous effusions: experience with 105 patients, J. Vasc. Interv. Radiol. 25 (9) (2014) 1398–1404.

e TECHNICAL REPORT

Paravertebral Catheter Placement, Under Direct Vision, for Postthoracotomy Analgesia

Tristam Brown, MBBS, BMedSc, Trevor J. D'Netto, MBBS (Hons), Gregory L. Falk, MBBS, FRACS, FACS, and Stephanie Phillips, BMed, FRCA, FANZCA

Key Words: analgesia, pain management, anesthetics, local, esophagectomy, thoracotomy

(*Surg Laparosc Endosc Percutan Tech* 2015;25:e170–e171)

Postthoracotomy pain can be severe and effective analgesia reduces postoperative pulmonary complications.[1] Although the gold standard for postthoracotomy pain management has been epidural analgesia[2] there is a trend toward paravertebral blockade (PVB) due to its simplicity and safety. PVB analgesia is comparable with epidural analgesia,[3] but has a lower failure rate, a lower incidence of vomiting and urinary retention,[4] and greater hemodynamic stability.[5,6] We describe an intraoperative technique of PVB catheter placement for use with continuous infusion, which in our esophagectomy patient cohort, has proved quick, safe, and effective.

A 2-mm skin incision is made 2 intercostal spaces below and medial to the thoracotomy incision and lateral to the spinous processes. The paraspinal fascia is penetrated with a Crile forceps and the depth to pleura noted. The catheter is introduced using an 11-G, 30.48-cm, ON-Q* Tunneler (ON-Q Kimberley Clark N.V., Da Vincilaan 1, Zaventem, Belguim) and peel apart sheath, which is bent to 30 degrees about 5 to 7 cm from the tip (this distance corresponding to the thickness of the chest wall noted on previous insertion of the Crile forceps). The introducer passes through the skin incision and muscle layers until the tip is palpable or visible deep to the parietal pleura. To maximize effectiveness of analgesia, care must be taken to not puncture the pleura at this point.[7] A plane between chest wall and parietal pleura is developed in the paravertebral sulcus, the full length of the introducer (15 cm). The bend in the introducer will need to be progressively increased to maintain its subpleural position (Fig. 1). Dissection is facilitated by small oscillations of the introducer, so that the tip moves across the chest wall beneath the pleura in an arc like manner, forming an elliptical space between the 2 layers. The process can be further facilitated by injection of saline or local anesthetic solution through the introducer, lifting the pleura from its muscular attachments.

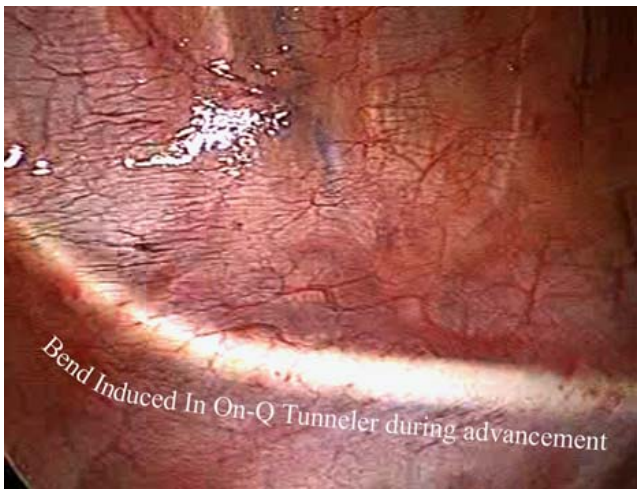


FIGURE 1. On-Q Tunneler dissecting between the parietal pleura from the muscular layer.

Once the tip of the introducer is positioned 2 intercostal spaces cephalad to the incision, the stylette is removed and a primed ON-Q* Catheter is advanced the full length of the sheath, held in place externally with forceps, and the pull apart sheath removed (Fig. 2). The catheter is sutured in place and connected to an elastomeric pump, loaded with 550 mL of 0.2% ropivacaine, with a fixed rate of 5 mL/h or other infusion according to local practice.

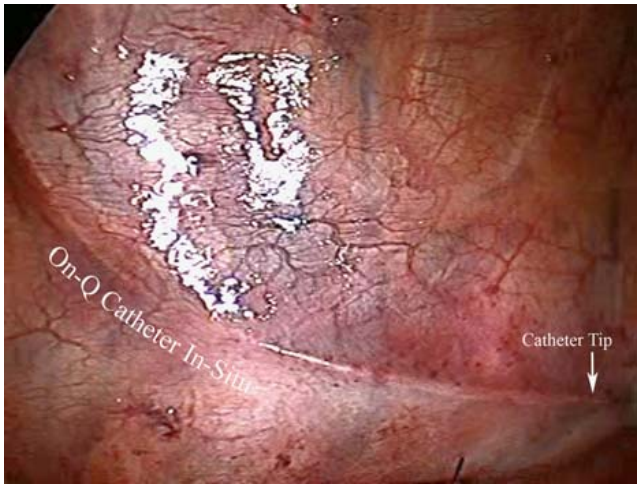


FIGURE 2. On-Q Catheter in situ.

Received for publication July 8, 2015; accepted August 16, 2015.
From the Sydney Adventist Hospital, Sydney, NSW, Australia.
The authors declare no conflicts of interest.
Reprints: Gregory L. Falk, MBBS, FRACS, FACS, Sydney Heartburn Clinic, Suite 29, 12 Tryon Road, Lindfield, NSW 2070, Australia (e-mail: sydney.heartburn@gmail.com).
Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Website, www.surgical-laparoscopy.com.

The technique is equally useful for thoracoscopic procedures.

Supplemental Digital Content 1 (MP4 Video 1, http://links.lww.com/SLE/A133) details the procedure.

REFERENCES

1. Muehling BM, Halter GL, Schelzig H, et al. Reduction of postoperative pulmonary complications after lung surgery using a fast track clinical pathway. *Eur J Cardiothorac Surg*. 2008;34:174–180.
2. Davies RG, Myles PS, Graham JM. A comparison of the analgesic efficacy and side-effects of paravertebral vs epidural blockade for thoracotomy—a systematic review and meta-analysis of randomized trials. *Br J Anaesth*. 2006;96:418–426.
3. Ding X, Jin S, Niu X, et al. A comparison of the analgesia efficacy and side effects of paravertebral compared with epidural blockade for thoracotomy: an updated meta-analysis. *PLoS One*. 2014;9:5.
4. El-Morsy G, El-Desouky T, Elsharkawy A, et al. Can thoracic paravertebral block replace thoracic epidural block in pediatric cardiac surgery? A randomized blinded study. *Ann Card Anaesth*. 2012;15:259–263.
5. Pintaric TS, Potocnik I, Hadzic A, et al. Comparison of continuous thoracic epidural with paravertebral block on perioperative analgesia and hemodynamic stability in patients having open lung surgery. *Reg Anesth Pain Med*. 2011;36:256–260.
6. Kotzé A, Scally A, Howell S. Efficacy and safety of different techniques of paravertebral block for analgesia after thoracotomy: a systematic review and metaregression. *Br J Anaesth*. 2009;103:626–636.
7. Komatsu T, Sowa T, Kino A, et al. The importance of pleural integrity for effective and safe thoracic paravertebral block: a retrospective comparative study on postoperative pain control by paravertebral block. *Interact Cardiovasc Thorac Surg*. 2015;20:296–299.

Symptoms, investigations and management of patients with cancer of the oesophagus and gastro-oesophageal junction in Australia

Bernard M Smithers, Paul P Fahey, Tracie Corish, David C Gotley, Gregory L Falk, Garett S Smith, George K Kiroff, Andrew D Clouston, David I Watson and David C Whiteman

ABSTRACT

Objective: To document presenting symptoms, investigations and management for Australian patients with oesophageal adenocarcinoma (OAC), gastro-oesophageal junction adenocarcinoma (GOJAC) and oesophageal squamous cell carcinoma (OSCC).

Design, setting and participants: Cross-sectional study of a population-based sample of 1100 Australian patients aged 18–79 years with histologically confirmed oesophageal cancer diagnosed in 2002–2005, using data from cancer registries and treatment centres, supplemented with clinical information collected through medical record review in 2006–2007 and mortality information collected in 2008.

Main outcome measures: Prevalence of primary symptoms, and staging investigations and treatment modalities used.

Results: The primary presenting symptom was dysphagia, which was self-reported by 41%, 39% and 48% of patients with OAC, GOJAC and OSCC, respectively. Less common symptoms were reflux, chest pain, bleeding and weight loss. All patients underwent endoscopy, most had a staging computed tomography scan (OAC 93%, GOJAC 95% and OSCC 93%), and about half had positron emission tomography scans (OAC 51%, GOJAC 44% and OSCC 42%). Pretreatment tumour stage was reported in 25% of records, and could be derived from results of investigations in a further 23%, but the remaining half lacked sufficient information to ascribe a pretreatment stage. Curative treatments were attempted for 60% of OAC, 88% of GOJAC and 65% of OSCC patients. Surgery was performed on 52% of OAC, 83% of GOJAC and 41% of OSCC patients. About two-thirds of surgical patients received additional therapies.

Conclusions: With anticipated increases in oesophageal cancer incidence, the resources required to diagnose and manage patients with oesphageal cancer are also likely to rise. Our data provide a baseline from which to plan for the future care of patients with cancers of the oesophagus.

MJA 2010; 193: 572–577

In Australia, oesophageal cancer represents 1.2% of all cancers and is responsible for 2.1% of cancer deaths. Recently, there has been a striking increase in oesophageal adenocarcinoma (OAC) incidence, estimated at 4.2% per year in New South Wales,[1] whereas the incidence of oesophageal squamous cell carcinoma (OSCC) has declined. Almost all of the increase in OAC incidence has occurred in males, contributing to a male–female ratio approaching 8 to 1.[1] Gastro-oesophageal junction adenocarcinoma (GOJAC) has also increased in incidence. The incidence patterns for OAC and GOJAC contrast with those for OSCC. This parallels trends observed in other Western countries[2,3] and is not due to changes in diagnostic criteria.[4] The principal causes of the increase in OAC (and probably GOJAC) are thought to be increased prevalence of gastro-oesophageal acid reflux and obesity in Western populations.[5-11] Changing patterns of obesity appear to be driving the rising incidence of OAC, with particular attention focusing on "male pattern" central adiposity, which is postulated to increase the production of mitogenic, obesity-related hormones.[12,13] Falling rates of *Helicobacter pylori* infection may also play a role, as chronic infection causes hypochlorhydria and thus protects against reflux-mediated carcinogenesis.[14]

The prognosis for patients diagnosed with these cancers is poor; 1-year survival for patients with OAC in a NSW study was 49% for localised cancer, 43% for cancers with regional spread and 12% for disseminated cancers.[1] Yet despite the rapid increases in incidence and the poor survival from oesophageal cancers, relatively little is known about the patterns of care for patients with these diseases. Here we report the findings of an investigation into the presentation and clinical management of a cohort of patients with carcinomas of the oesophagus or gastro-oesophageal junction.

METHODS

Our study was based on a cohort of patients previously enrolled in the Australian Cancer Study (ACS), a population-based, case–control study undertaken to investigate risk factors for oesophageal cancer.[6] For our study (the ACS Clinical Follow-up Study), we collected clinical information and outcome data on ACS patients. We collected data on the presenting symptoms of patients, investigations and treatment pathways.

Patients

For the ACS, all patients aged 18–79 years with a histologically confirmed primary invasive cancer of the oesophagus or gastro-oesophageal junction diagnosed between 1 July 2002 (1 July 2001 in Queensland) and 30 June 2005 in mainland Australia were identified. Full details of recruitment of patients into the ACS have been described elsewhere.[6] Briefly, patients were ascertained principally via systematic review of admissions and clinic registers at major treatment centres throughout Australia; additional cases were identified by cancer registries (cancer notification is mandatory in all states). Histological details were abstracted from pathology reports. Anatomical sites of adenocarcinoma tumours were categorised according to the World Health Organization classification into "oesophageal" and "oesophago-gastric junction" tumours.[15] For analysis, we compared patients with OAC, GOJAC and OSCC.

Our study was approved by the Human Research Ethics Committee of the Queensland Institute of Medical Research and the ethics committees of participating hospitals. All participants gave their informed consent to take part.

Data collection

Two sources of data were used: prediagnostic symptom information self-reported by patients at the time of their recruitment into the ACS, and clinical and treatment information obtained from each patient's medical records.

Thus, patients self-completed a questionnaire on recruitment into the ACS (2002–2005), followed shortly after by a standardised interview to elicit details of symptom history, presentation, and pathway to diagnosis. Case–control analyses to identify risk factors for oesophageal cancer have been reported separately.[5-7]

Clinical data were abstracted from each patient's medical records by trained nurses in 2006–2007 and entered on standardised case report forms. Medical records included hospital files and reports from private practitioners and pathology, radiology, and other imaging services. Information was collected on presenting symptoms, diagnostic and staging investigations, clinical stage of disease, and management. For the latter, details were recorded regarding chemotherapy, radiotherapy, other endoscopic treatments and surgery that the patient received. Outcome information was also collected, including details of dates of admission, discharge (or death) for each episode of treatment, date of last recorded outpatient attendance, and disease status.

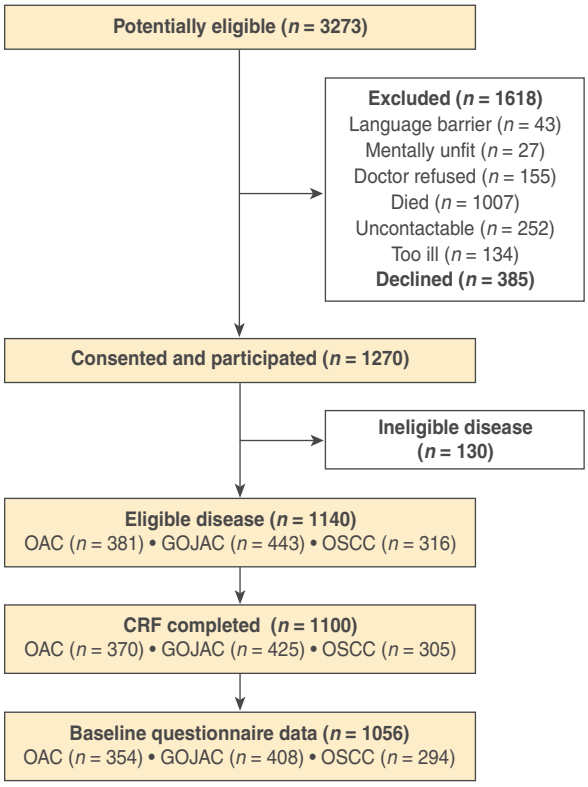
Case report forms were returned to the Queensland Institute of Medical Research for data coding and checking. Summary variables were derived from primary variables for analysis. We used the American Joint Committee on Cancer (AJCC) tumour stage classification for oesophageal cancer, when reported. For cases with missing stage data, we attempted to impute the stage using available information.

We assigned each participant an index of remoteness and accessibility to services based on their residential postcode using the 2006 Accessibility/Remoteness Index of Australia codes from the Australian Government Department of Health and Ageing (http://www9.health.gov.au/aria/ariainpt.cfm).

Data analysis

We compared age distributions across subtypes using one-way analysis of variance. For categorical variables, we used the χ^2 test. Analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC, USA), statistical significance was assumed at the 5% level, and no adjustments were made for multiple comparisons.

1 Recruitment of patients into the ACS Clinical Follow-up Study



ACS = Australian Cancer Study. CRF = case report form. GOJAC = gastro-oesophageal junction adenocarcinoma. OAC = oesophageal adenocarcinoma. OSCC = oesophageal squamous cell carcinoma. ◆

RESULTS

We identified 3273 potentially eligible patients with oesophageal cancer, of whom 1618 were excluded for various reasons and 385 declined to participate (Box 1). Of the remaining 1270, 1140 patients had histologically confirmed oesophageal cancer and gave consent for access to their medical records. Completed case report forms were available for 1100 patients (370 OAC, 425 GOJAC and 305 OSCC) and linked questionnaire data were available for 1056 patients.

Patient demographics are shown in Box 2. Notably, age distributions were similar for the three patient groups, whereas sex distributions were markedly different for OSCC patients compared with OAC and GOJAC patients. Eighty-seven per cent of patients resided in cities and towns, 11% lived in moderately accessible regional locations, and 2% were from remote or very remote locations.

Presenting symptoms

Interview data describing medical presentation and symptom history were available for 831 patients. The primary symptom for which the patient sought medical attention, the prevalence of all symptoms volunteered by the patient, and the prevalence of symptoms as elicited and recorded by the doctor are shown in Box 3. Dysphagia, the most frequent primary symptom, was self-reported by 41%–48% of patients. Gastro-oesophageal acid reflux was self-reported by 7%–9% of patients as the primary reason for presentation but elicited by a doctor in 46% of OAC and 44% of GOJAC patients. As recorded by the doctor, OSCC patients had a higher prevalence of odynophagia than OAC or GOJAC patients, but less reflux. Odynophagia, epigastric pain, chest pain and weight loss were all uncommon reasons for presentation, but were commonly found to be present on direct questioning. Eight per cent and 3% of OAC and GOJAC patients, respectively, were diagnosed through Barrett's oesophagus surveillance programs, and 2%–4% of OAC, GOJAC and OSCC diagnoses were incidental findings from routine health checks.

Investigations

All patients had undergone upper gastrointestinal endoscopy as an eligibility criterion for our study (Box 4). A computed tomography (CT) scan was performed in 93%–95% of patients, a fluorodeoxyglucose positron emission tomography (FDG-PET) scan in 42%–51% of patients, and endoscopic ultrasound (EUS) in 20%–21% of patients. Laparoscopy was more commonly performed in the GOJAC group than the OAC and OSCC groups.

Pretreatment staging

An AJCC stage was reported in 7% of patient records (range, 5%–10%) (Box 5); converting tumour–node–metastasis (TNM) codes into AJCC tumour stages increased the overall proportion of patients with stage data to 25% (range, 23%–27%). Imputation using the FDG-PET scan result for M status and EUS for T and N status increased the overall proportion of patients with stage data to

2 Demographic characteristics of patients in the ACS Clinical Follow-up Study*

Characteristic	OAC (*n* = 370)	GOJAC (*n* = 425)	OSCC (*n* = 305)	*P*
Mean age (SD) at diagnosis, years	63.5 (9.6)	63.3 (9.7)	64.7 (9.3)	0.14
Men	334 (90%)	370 (87%)	172 (56%)	< 0.001
Education†				< 0.001
School only	167 (47%)	167 (41%)	165 (56%)	
Technical college or diploma	165 (47%)	198 (49%)	103 (35%)	
University degree	22 (6%)	43 (11%)	26 (9%)	
Location‡				0.14
Highly accessible or accessible	304 (85%)	365 (88%)	248 (86%)	
Moderately accessible	40 (11%)	44 (11%)	35 (12%)	
Remote or very remote	13 (4%)	4 (1%)	6 (2%)	

ACS = Australian Cancer Study. GOJAC = gastro-oesophageal junction adenocarcinoma. OAC = oesophageal adenocarcinoma. OSCC = oesophageal squamous cell carcinoma. * Data are number (%) except where otherwise specified. † Education self-reported in questionnaires returned by 354 OAC, 408 GOJAC and 294 OSCC patients. ‡ Based on residential postcodes using the 2006 Accessibility/Remoteness Index of Australia. Data were missing for 41 patients. ◆

49% (range, 47%–50%). However, for about half of the patients, there were insufficient data to estimate pretreatment cancer stage.

Treatment

Curative treatments were attempted for 60% (222/370) of OAC, 88% (372/425) of GOJAC, and 65% (197/305) of OSCC patients. Overall, 72% of patients were treated with curative intent, of whom the majority (61%) had surgical resection (Box 6). Of patients offered curative therapy, those with OAC or GOJAC were more likely to have surgery than those with OSCC. Among surgical patients, preoperative (neoadjuvant) therapy was performed on similar proportions of patients with OAC, GOJAC and OSCC. Preoperative chemoradiotherapy (CRT) was used more commonly than preoperative chemotherapy alone. Postoperative therapy was performed most frequently for patients with GOJAC followed by patients with OSCC and those with OAC.

The most common palliative therapy was CRT. Stents were used for 168 patients (for 98 patients as immediate palliative treatment, and for 70 patients after initial attempts at curative treatment). No patient who had a resection had a stent inserted.

DISCUSSION

Our study provides the first comprehensive description of the presentation and management of Australian patients with oesophageal cancer. The cohort is not entirely representative, as enrolment into the study required a number of time-limiting steps, which meant that records for some potentially eligible patients could not be reviewed. For example, patients with late-stage disease (AJCC stages III or IV) were less likely to be enrolled, and we could not access files for patients who died before written consent could be obtained. This means that we may have underestimated the prevalence of such tumours, and thus probably overestimated the proportions of patients offered curative therapies.

Nonetheless, our study provides the first overall "snapshot" of these cancers and their management in Australia. The sample was also large, comprising an estimated 35% of all people in mainland Australia diagnosed with oesophageal cancer during the study period.

In a country defined by large distances and a dispersed population, the issue of access is important. Reassuringly, we found the geographical distribution of this cohort was similar to that of the 2001 census.

The most common presenting symptom was dysphagia, which on direct questioning was found to be present in over 70% of patients, a proportion similar to that found in other studies.[16,17] Dysphagia occurs when the oesophageal circumference has been reduced by two-thirds,[18] which is sufficient to compromise the lumen. The United Kingdom guidelines for managing oesophageal cancer outline a number of "alarm symptoms", of which dysphagia is the first, and for which referral for endoscopy is recommended within 2 weeks of presentation.[19] Our data suggest most patients do not recognise the importance of dysphagia as an alarm symptom. Only 7%–9% of patients reported reflux as their primary symptom, a similar proportion to that reported in a

3 ACS Clinical Follow-up Study: reasons for presentation self-reported by patient* and recorded by doctor in clinical files

	Primary reason self-reported by patient			All reasons self-reported by patient				All reasons recorded by doctor†			
Symptom	OAC (*n* = 291)	GOJAC (*n* = 317)	OSCC (*n* = 223)	OAC (*n* = 291)	GOJAC (*n* = 317)	OSCC (*n* = 223)	*P*	OAC (*n* = 370)	GOJAC (*n* = 425)	OSCC (*n* = 305)	*P*
Odynophagia	11 (4%)	16 (5%)	12 (5%)	29 (10%)	31 (10%)	26 (12%)	0.752	62 (17%)	93 (22%)	107 (35%)	< 0.001
Dysphagia	119 (41%)	125 (39%)	106 (48%)	156 (54%)	169 (53%)	138 (62%)	0.095	261 (71%)	294 (69%)	255 (84%)	< 0.001
Epigastric pain	9 (3%)	6 (2%)	5 (2%)	15 (5%)	12 (4%)	10 (4%)	0.716	87 (24%)	100 (24%)	82 (27%)	0.567
Reflux‡	23 (8%)	30 (9%)	16 (7%)	36 (12%)	45 (14%)	28 (13%)	0.768	170 (46%)	188 (44%)	85 (28%)	< 0.001
Weight loss	3 (1%)	7 (2%)	7 (3%)	17 (6%)	24 (8%)	22 (10%)	0.233	184 (50%)	184 (43%)	157 (51%)	0.062
Bleeding	15 (5%)	9 (3%)	3 (1%)	18 (6%)	14 (4%)	6 (3%)	0.168	25 (7%)	25 (6%)	6 (2%)	0.012
Chest pain	13 (4%)	15 (5%)	8 (4%)	27 (9%)	23 (7%)	15 (7%)	0.505	19 (5%)	21 (5%)	19 (6%)	0.727
Other	64 (22%)	81 (26%)	52 (23%)	85 (29%)	128 (40%)	80 (36%)	0.015	88 (24%)	112 (26%)	73 (24%)	0.645

ACS = Australian Cancer Study. GOJAC = gastro-oesophageal junction adenocarcinoma. OAC = oesophageal adenocarcinoma. OSCC = oesophageal squamous cell carcinoma. * Symptoms self-reported by patient at telephone interview. † Number of patients with missing data in each category: odynophagia (26), dysphagia (25), epigastric pain (27), reflux (28) and weight loss (25). ‡ Gastro-oesophageal acid reflux. ◆

4 ACS Clinical Follow-up Study: investigations

Pretreatment	OAC ($n = 370$)	GOJAC ($n = 425$)	OSCC ($n = 305$)	P
Endoscopy	370 (100%)	425 (100%)	305 (100%)	
CT scan	344 (93%)	402 (95%)	284 (93%)	0.589
FDG-PET scan	187 (51%)	187 (44%)	127 (42%)	0.050
EUS	74 (20%)	91 (21%)	61 (20%)	0.853
Laparoscopy	57 (15%)	123 (29%)	31 (10%)	< 0.001
Barium swallow	46 (12%)	50 (12%)	55 (18%)	0.035
Bronchoscopy	4 (1%)	6 (1%)	24 (8%)	< 0.001
Other investigation	151 (41%)	169 (40%)	130 (43%)	0.740

ACS = Australian Cancer Study. CT = computed tomography. EUS = endoscopic ultrasound. FDG-PET = fluorodeoxyglucose positron emission tomography. GOJAC = gastro-oesophageal junction adenocarcinoma. OAC = oesophageal adenocarcinoma. OSCC = oesophageal squamous cell carcinoma. ◆

previous study.[16] The underlying precipitant for these patients may have been a change, likely worsening, of previous reflux symptoms or the development of new symptoms.

A key finding was the infrequent recording of AJCC pretreatment tumour stage (7%), and although stage could be imputed for a further 42%, for about half of the patients it was impossible to determine the extent of their cancer. Of the staging investigations employed, CT scans were the most common, being used in more than 90% of patients in our study. The major benefit of CT is the ability to rapidly identify patients with distant metastases. Staging information is improved by also performing an EUS to assess local infiltration and local nodal status. Relatively few Australian centres were performing EUS at the time of our study, hence the low usage we observed. Compared with conventional staging modalities, FDG-PET scanning has been shown to detect distant metastases in 4%–28% of oesophageal cancer patients and to change management in 3%–40% of patients.[20] Although fewer centres were performing FDG-PET than EUS in Australia at the time of our study, FDG-PET scans were reported for 42%–51% of the patients. Thus, despite limited availability, both FDG-PET scanning and EUS were performed on sizeable numbers of patients, suggesting rapid uptake for these modalities.

Putting aside the extent of incomplete reporting, our study differs from others in having relatively fewer patients with stage IV cancers. For example, a United States study reported stage IV disease in 48% of OAC patients and 52% of GOJAC patients[21] — considerably higher than the proportions we observed. Reporting of cancer stage is not mandatory in Australia, hence there are no reliable population-based data for comparison. Instead, estimates of the distribution of cancer stage must be derived from chart reviews. As the use of chart reviews requires patient consent, and because consent is less likely among patients with late-stage disease, it is likely that all studies based on chart review will underestimate the incidence of late-stage disease.

We identified apparent differences in the surgical management of OAC and GOJAC. Specifically, our data suggest that patients with GOJAC are more likely to undergo surgery alone than OAC or OSCC patients. A similar finding was reported in an Irish study.[22] Information bias may partly explain these differences, as the location of a tumour can be identified more precisely from surgical resection specimens than from endoscopy. Thus, patients who have undergone surgery are more likely to have the anatomical location of their tumour classed as gastro-oesophageal junction than patients who have not received surgery.

The proportion of surgical patients undergoing preoperative (neoadjuvant) therapy in our study was lower than the proportion in the US study[21] but higher than that found in the Irish study.[22] At the time that the patients in our study were being treated, there had been one international report of benefit from neoadjuvant CRT in patients with OAC,[23] and one account of benefit from preoperative chemotherapy in both OAC and OSCC patients.[24] An Australian phase II study assessing the role of neoadjuvant CRT and CRT alone for cure and palliation of OAC and OSCC had

5 ACS Clinical Follow-up Study: pretreatment staging

Pretreatment AJCC tumour stage	OAC ($n = 370$)	GOJAC ($n = 425$)	OSCC ($n = 305$)
Recorded by doctor			
Total available*	36 (10%)	21 (5%)	19 (6%)
Imputed from doctor's record of TNM codes			
T-stage (T1, T2, T3, T4) recorded by doctor	105 (28%)	129 (30%)	100 (33%)
N-stage (N0, N1) recorded by doctor	106 (29%)	126 (30%)	102 (33%)
M-stage (M0, M1) recorded by doctor	83 (22%)	99 (23%)	83 (27%)
Total available†	99 (27%)	99 (23%)	80 (26%)
Imputed from doctor's record of TNM codes and clinical test results			
T-score from EUS	67 (18%)	84 (20%)	54 (18%)
N-score from EUS	68 (18%)	81 (19%)	53 (17%)
M-score from FDG-PET scan	178 (48%)	177 (42%)	123 (40%)
Total available‡	186 (50%)	208 (49%)	142 (47%)
Stage	($n = 186$)	($n = 208$)	($n = 142$)
I	20 (11%)	26 (13%)	15 (11%)
II	53 (28%)	79 (38%)	51 (35%)
III	43 (23%)	74 (36%)	43 (30%)
IV	70 (38%)	29 (14%)	33 (23%)
Total	186 (100%)	208 (100%)	142 (100%)

ACS = Australian Cancer Study. AJCC = American Joint Committee on Cancer. EUS = endoscopic ultrasound. FDG-PET = fluorodeoxyglucose positron emission tomography. GOJAC = gastro-oesophageal junction adenocarcinoma. OAC = oesophageal adenocarcinoma. OSCC = oesophageal squamous cell carcinoma. TNM = tumour–node–metastasis. * At least AJCC stage I, II, III or IV. † Doctor's record of AJCC stage augmented by doctor's record of TNM code where available. ‡ Doctor's record of AJCC stage augmented by doctor's record of TNM code and endoscopic ultrasound and FDG-PET findings where available. ◆

6 ACS Clinical Follow-up Study: treatment

Treatment	OAC* (*n* = 370)	GOJAC (*n* = 425)	OSCC (*n* = 305)	*P*
No surgery	175 (48%)	72 (17%)	180 (59%)	< 0.001
Surgery	193 (52%)	353 (83%)	125 (41%)	
Treated with curative intent†				< 0.001‡
Definitive chemotherapy and radiotherapy§	29 (13%)	19 (5%)	72 (37%)	
Resection alone	72 (32%)	150 (40%)	48 (24%)	
Resection and neoadjuvant therapy				
Resection and preoperative radiotherapy	0	0	1 (< 1%)	
Resection and preoperative chemotherapy	22 (10%)	32 (9%)	5 (3%)	
Resection and preoperative chemotherapy and radiotherapy	48 (22%)	49 (13%)	27 (14%)	
Resection and adjuvant therapy				
Resection and postoperative radiotherapy	6 (3%)	11 (3%)	13 (7%)	
Resection and postoperative chemotherapy	7 (3%)	41 (11%)	3 (2%)	
Resection and postoperative chemotherapy and radiotherapy	17 (8%)	48 (13%)	14 (7%)	
Resection and combined therapy				
Resection and preoperative and postoperative chemotherapy	3 (1%)	7 (2%)	2 (1%)	
Resection and other combinations	18 (8%)	15 (4%)	12 (6%)	
Total	*222 (100%)*	*372 (100%)*	*197 (100%)*	
Not treated or treated without curative intent§				
No treatment	24 (17%)	3 (6%)	6 (6%)	
Radiotherapy alone	19 (13%)	5 (10%)	16 (15%)	
Chemotherapy alone	24 (17%)	17 (34%)	4 (4%)	
Chemotherapy and non-curative radiotherapy¶	76 (53%)	25 (50%)	80 (75%)	
Total	*143 (100%)*	*50 (100%)*	*106 (100%)*	

ACS = Australian Cancer Study. OAC = oesophageal adenocarcinoma. GOJAC = gastro-oesophageal junction adenocarcinoma. OSCC = oesophageal squamous cell carcinoma. * Two patients in OAC group had missing data on surgery. † Data missing on whether curative or not for three patients in OAC group, three in GOJAC group, and two in OSCC group. ‡ Comparison of curative versus non-curative treatment. § Curative radiotherapy (≥ 50 Gy) targeting the oesophagus. ¶ Non-curative radiotherapy (< 50 Gy) or not targeted at oesophagus. ◆

also been reported before our assessment.[25] It is likely that these publications, along with an active Australian trial of preoperative CRT,[26] raised awareness among Australian clinicians who treat such patients. This could explain the high prevalence of neoadjuvant therapy for OAC and OSCC, and may also explain why 10% of patients in our study were also enrolled in trials. While there is no evidence from trials that routine postoperative therapy improves survival, we observed reasonably high proportions of patients undergoing postoperative therapy. The reasons for this were not clear from the records.

We found that use of definitive CRT in our study was markedly higher for patients with OSCC (37%) than for patients with OAC (13%) or GOJAC (5%). In comparison, the Irish study observed proportions of patients undergoing definitive CRT as 12% for OAC, 6% for GOJAC and 12% for OSCC.[22] A possible explanation for the difference may be a widespread perception among clinicians that adenocarcinomas are less sensitive to radiation than squamous cell carcinomas. There are limited data to determine the validity of this perception; however, there are more publications reporting benefits for CRT as an alternative to resection for OSCC[27,28] than as a treatment for OAC.

From our observation, most patients present with late-stage disease, although precise staging information is infrequently recorded. We encourage efforts to increase the reporting of tumour stage for these cancers. Although dysphagia is common, it is not apparently recognised as an alarm symptom; education to rectify this deficiency may be warranted. Many patients are managed by teams comprising surgeons and medical and radiation oncologists. With the increasing use of combined modality treatment, and the need to use technologies such as EUS and FDG-PET scanning, it would seem that optimal patient management will be through specialist centres with a suitable caseload and interest in the disease. The incidence of OAC and GOJAC is rising rapidly in Australia, a factor which must be considered when planning for future health service needs. Finally, given the high proportion of patients with late-stage disease, and the acknowledged poor survival rates for these cancers, we need to continue to explore ways to reduce the disease burden through primary prevention and early detection.

ACKNOWLEDGEMENTS

Our study was supported by the Cancer Council Queensland and the National Health and Medical Research Council. David Whiteman is supported by a Future Fellowship from the Australian Research Council. The funding bodies played no role in the design or conduct of the study; the collection, management, analysis or interpretation of the data; or preparation, review or approval of the manuscript. We thank Shahram Sadeghi for assistance with pathology abstractions, and Nirmala Pandeya for data cleaning and programming. The study investigators were David Whiteman, Adele Green, David Gotley, B Mark Smithers, David Watson, Gregory Falk, Garett Smith, George Kiroff, Steven Archer, Nicholas Hayward and Andrew Clouston; the project manager was Tracie Corish; the database managers were Karen Harrap and Troy Sadkowski; and the research nurses were Janine Thomas, Ellen Minehan, Deborah Roffe, Sue O'Keefe, Suzanne Lipshut, Gabby Connor, Hayley Berry, Linda Terry, Michael Connard, Leanne Bowes, MaryRose Malt and Jo White. The clinical contributors were: *Australian Capital Territory* — Charles Mosse and Noel Tait; *New South Wales* — Chris Bambach, Andrew Biankan, Roy Brancatisano, Max Coleman, Michael Cox, Stephen Deane, James Gallagher, Mike Hollands, Tom Hugh, David Hunt, John Jorgensen, Christopher Martin, Mark Richardson, Ross Smith and David Storey; *Queensland* — John Avramovic, John Croese, Justin D'Arcy, Stephen Fairley, John Hansen, John Masson, Ian Martin, Les Nathanson, Barry O'Loughlin, Leigh Rutherford, Richard Turner and Morgan Windsor; *South Australia* — Justin Bessell, Peter Devitt and Glyn Jamieson; *Victoria* — Stephen Blamey, Alex Boussioutas, Richard Cade, Gary Crosthwaite, Ian Faragher, John Gribbin, Geoff Hebbard, Bruce Mann, Bob Millar, Paul O'Brien, Robert Thomas and Simon Wood; *Western Australia* — Kingsley Faulkner and Jeff Hamdorf.

COMPETING INTERESTS

None identified.

AUTHOR DETAILS

Bernard M Smithers, MB BS, FRACS, FRCS, Associate Professor of Surgery[1]
Paul P Fahey, BSc, MMedStat, Biostatistician[2]
Tracie Corish, RN, Research Nurse[2]
David C Gotley, MD, FRACS, Professor of Surgery[1]
Gregory L Falk, FRACS, FACS, Clinical Associate Professor of Surgery[3]
Garett S Smith, MS, FRACS, Clinical Associate Professor of Surgery[4]
George K Kiroff, MB BS, MS, FRACS, Surgeon[5]
Andrew D Clouston, MB BS, PhD, FRCPA, Pathologist[6]
David I Watson, MD, FRACS, Professor[7]
David C Whiteman, MB BS,PhD, FAFPHM, Senior Principal Research Fellow[2]

1 Upper GI and Soft Tissue Unit, Division of Surgery, Princess Alexandra Hospital, Brisbane, QLD.
2 Queensland Institute of Medical Research, Brisbane, QLD.
3 Concord Repatriation General Hospital, Sydney, NSW.
4 University of Sydney Northern Clinical School, Royal North Shore Hospital, Sydney, NSW.
5 Geelong Hospital, Geelong, VIC.
6 Envoi Specialist Pathologists, Brisbane, QLD.
7 Department of Surgery, Flinders University, Adelaide, SA.

Correspondence:
david.whiteman@qimr.edu.au

REFERENCES

1 Stavrou EP, McElroy HJ, Baker DF, et al. Adenocarcinoma of the oesophagus: incidence and survival rates in New South Wales, 1972–2005. *Med J Aust* 2009; 191: 310-314.
2 Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998; 83: 2049-2053.
3 Botterweck AA, Schouten LJ, Volovics A, et al. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. *Int J Epidemiol* 2000; 29: 645-654.
4 Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005; 97: 142-146.
5 Pandeya N, Webb PM, Sadeghi S, et al. Gastro-oesophageal reflux symptoms and the risks of oesophageal cancer: are the effects modified by smoking, NSAIDs or acid suppressants? *Gut* 2010; 59: 31-38.
6 Whiteman DC, Sadeghi S, Pandeya N, et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. *Gut* 2008; 57: 173-180.
7 Pandeya N, Williams GM, Sadhegi S, et al. Associations of duration, intensity, and quantity of smoking with adenocarcinoma and squamous cell carcinoma of the esophagus. *Am J Epidemiol* 2008; 168: 105-114.
8 Chow WH, Blot WJ, Vaughan TL, et al. Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst* 1998; 90: 150-155.
9 Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. *Ann Intern Med* 1999; 130: 883-890.
10 Mayne ST, Navarro SA. Diet, obesity and reflux in the etiology of adenocarcinomas of the esophagus and gastric cardia in humans. *J Nutr* 2002; 132 (11 Suppl): 3467S-3470S.
11 Vaughan TL, Davis S, Kristal A, Thomas DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 1995; 4: 85-92.
12 Garofalo C, Surmacz E. Leptin and cancer. *J Cell Physiol* 2006; 207: 12-22.
13 Kendall BJ, Macdonald GA, Hayward NK, et al. Leptin and the risk of Barrett's oesophagus. *Gut* 2008; 57: 448-454.
14 Blaser MJ. Disappearing microbiota: *Helicobacter pylori* protection against esophageal adenocarcinoma. *Cancer Prev Res (Phila)* 2008; 1: 308-311.
15 Spechler SJ, Dixon MF, Genta R, et al. Adenocarcinoma of the oesophago-gastric junction. In: Hamilton SR, Aaltonen LA, editors. Pathology and genetics of tumours of the digestive system. World Health Organization classification of tumours. Volume 2. Lyon: IARC Press, 2000.
16 Gibbs JF, Rajput A, Chadha KS, et al. The changing profile of esophageal cancer presentation and its implication for diagnosis. *J Natl Med Assoc* 2007; 99: 620-626.
17 Bytzer P, Christensen PB, Damkier P, et al. Adenocarcinoma of the esophagus and Barrett's esophagus: a population-based study. *Am J Gastroenterol* 1999; 94: 86-91.
18 DeMeester TR, Barlow AP. Surgery and current management for cancer of the esophagus and cardia: part I. *Curr Probl Surg* 1988; 25: 475-531.
19 Allum WH, Griffin SM, Watson A, Colin-Jones D. Guidelines for the management of oesophageal and gastric cancer. *Gut* 2002; 50 Suppl 5: v1-v23.
20 Salavati A, Basu S, Heidari P, Alavi A. Impact of fluorodeoxyglucose PET on the management of esophageal cancer. *Nucl Med Commun* 2009; 30: 95-116.
21 Cronin-Fenton DP, Mooney MM, Clegg LX, Harlan LC. Treatment and survival in a population-based sample of patients diagnosed with gastroesophageal adenocarcinoma. *World J Gastroenterol* 2008; 14: 3165-3173.
22 Cronin-Fenton DP, Sharp L, Carsin AE, Comber H. Patterns of care and effects on mortality for cancers of the oesophagus and gastric cardia: a population-based study. *Eur J Cancer* 2007; 43: 565-575.
23 Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. *N Engl J Med* 1996; 335: 462-467.
24 Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 2002; 359: 1727-1733.
25 Burmeister BH, Denham JW, O'Brien M, et al. Combined modality therapy for esophageal carcinoma: preliminary results from a large Australasian multicenter study. *Int J Radiat Oncol Biol Phys* 1995; 32: 997-1006.
26 Burmeister BH, Smithers BM, Gebski V, et al. Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial. *Lancet Oncol* 2005; 6: 659-668.
27 Chiu PW, Chan AC, Leung SF, et al. Multicenter prospective randomized trial comparing standard esophagectomy with chemoradiotherapy for treatment of squamous esophageal cancer: early results from the Chinese University Research Group for Esophageal Cancer (CURE). *J Gastrointest Surg* 2005; 9: 794-802.
28 Stahl M, Stuschke M, Lehmann N, et al. Chemoradiation with and without surgery in patients with locally advanced squamous cell carcinoma of the esophagus. *J Clin Oncol* 2005; 23: 2310-2317.

(Received 1 Mar 2010, accepted 3 Aug 2010) ❑

ORIGINAL ARTICLE

Ratio of Metastatic Lymph Nodes to Total Number of Nodes Resected is Prognostic for Survival in Esophageal Carcinoma

Clive J. Kelty, MB, ChB, PhD, FRCSEd, FRCS(Gen Surg), Catherine W. Kennedy, RMRA,† and Gregory L. Falk, MBBS, FRACS, FACS*†*

Introduction: The role of the number of metastatic nodes in esophageal cancer surgery is of interest. We assess predictors of survival after oesophagectomy for esophageal and gastroesophageal junction malignancy.

Methods: Prospective data of consecutive patients undergoing oesophagectomy and systematic lymphadenectomy between 1991 and 2007.

Results: Of 224 patients, 148 patients (66%) had adenocarcinoma, 70 (31%) squamous cell carcinoma, and 6 (2.6%) were other tumor types. Five-year survival was 43% with hospital mortality of 3.5%. Locoregional recurrence occurred in 14%. The total number of affected nodes significantly reduced survival (four or more metastatic nodes). Further analysis of the ratio of nodes affected to the total number resected showed a significant decrease in survival as the percentage of positive nodes increased ($p < 0.001$).

Conclusions: Patients undergoing surgery for esophageal cancer should be staged according to a minimum total number of metastatic lymph nodes and ratios because this more accurately predicts survival than current staging systems.

Key Words: Esophageal cancer, Esophagectomy, Lymphadenectomy, Staging.

(*J Thorac Oncol.* 2010;5: 1467–1471)

Adenocarcinoma of the esophagus is increasing in incidence more rapidly than any other cancer in the Western world.[1] The mainstay of treatment for this and squamous cell carcinoma remains surgical, namely esophagectomy, despite advances in other therapies. However, the overall prognosis for these patients is dismal, with survival in most countries around 10%. Outcomes after surgery are marginally better with reported 5-year survival rates averaging 25%.[2–4] It is known that these tumors spread radially via the lymphatic system, thus resection of the primary tumor and lymphadenectomy are advocated.[5] The rationale for lymphadenectomy is primarily based on the Japanese experience in gastric cancer. However, the evidence for this in esophageal carcinoma is less clear and remains a controversial issue.[6] Intuitively, the more radical the resection, the more lymph nodes (LNs) will be removed, and this will improve staging of the disease and possibly affect prognosis, either by reducing or delaying locoregional recurrence, or increasing the disease free survival. However, the extent of lymphadenectomy is not standardized among surgeons, and there is a lack of randomized trials assessing this issue.

The number of LNs removed during lymphadenectomy is of value, in particular the presence of LN metastases, because it seems that there is prognostic significance in the number of metastases This may have treatment implications. According to the Sixth International Union Against Cancer tumor node metastasis (TNM) classification (which is also uniform with the sixth edition of the American Joint Committee on Cancer staging), any regional LNs with metastatic involvement were staged as "N1."[7,8] However, this binary grading was controversial because there is increasing evidence to suggest that the number of metastatic nodes, rather than positive or negative metastatic nodes, may affect prognosis. It has been shown in several studies that increasing numbers of resected nodes with metastatic deposits is one of the most important prognostic factors; there is a significant reduction in survival after curative oesophagectomy for both squamous cell carcinoma and adenocarcinoma.[9–20] This was addressed by the seventh edition of the American Joint Committee on Cancer Staging Manual that was published in January 2010.[21] The new classification now recognizes different nodal classification (N1-3) based on coarse groupings of the number of nodes involved (0, 1–2, 3–6, and >7, respectively).

It has also been suggested that it is not simply the number of nodes that is important but that the LN yield needs to be adequate for staging[17–19]; the numbers suggested range from 10 to more than 18. This is in stark contrast to the sixth

*Department of Upper GI Surgery, Concord Repatriation General Hospital; and †Department of Surgery, University of Sydney, Strathfield Private Hospital Campus, Sydney, New South Wales, Australia.

Disclosure: The authors declare no conflicts of interest.

Address for correspondence: Clive J. Kelty, MB, ChB, PhD, FRCSEd, FRCS(Gen Surg), Department of Surgery, Doncaster Royal Infirmary, Armthorpe Road, Doncaster DN2 5LT, United Kingdom. E-mail: clive.kelty@bigfoot.com

Presented in part to Association of Upper Gastrointestinal Surgeons, Cardiff, September 2007 and Society of American Gastrointestinal and Endoscopic Surgeons, Philadelphia, April 2008.

ISSN: 1556-0864/10/0509-1467

TNM classification that only required six nodes.[7] This was not specifically addressed in the seventh edition; however, it states that an adequate lymphadenectomy requires between 12 and 22 nodes and advocates as extensive a lymphadenectomy as possible.

What remains less clear, however, is whether it is simply the absolute number of metastatic nodes that is important or whether the ratio of affected nodes to nodes resected may be an independent prognostic factor.

We currently perform a systematic two-field lymphadenectomy that has been reported previously.[22] Therefore, we examined survival in a contemporary cohort of patients diagnosed with esophageal carcinoma who underwent an en-bloc lymphadenectomy, and whether the extent of LN metastases, in particular the ratio of nodes affected compared with the total yield of resected nodes, had a prognostic effect on survival.

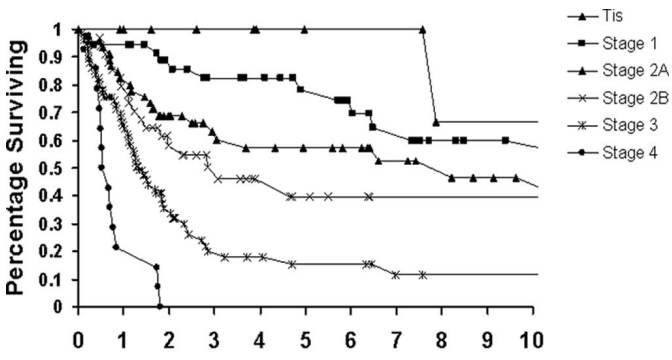
METHODS

A prospective database of patients who had carcinoma of the esophagus and gastroesophageal junction (excluding proximal lesions and Siewert type III adenocarcinomas) and who underwent subtotal oesophagectomy and systematic lymphadenectomy in a tertiary referral center between 1991 and 2007 was collected. Routine preoperative evaluation included upper gastrointestinal endoscopy with biopsy, computerized tomography scan, and selective endoscopic ultrasound. Staging laparoscopy was also performed on a selective basis for junctional (Siewert II) tumors. Operative fitness was determined by clinical assessment, pulmonary function testing, arterial blood gas, and cardiac imaging, as clinically indicated. All patients fit for surgery and assessed as feasible for R0 resection despite evidence of nodal disease on imaging were offered surgical resection on an all-comers policy. Latterly in the series, patients were offered neoadjuvant therapy if the tumor was considered borderline resectable (borderline attachment to pleura, pericardium or aorta or bulky tumors and adjacent lymphadenopathy) on preoperative staging. This constituted three cycles of ECX (epirubicin, cisplatin, and capecitabine) in adenocarcinomas and two cycles of cisplatin and 5-fluouracil in squamous tumors. The surgical procedure comprised Ivor-Lewis oesophagogastrectomy and systematic two-field en-bloc lymphadenectomy. All patients had given prior consent for data to be collected on the database. We assessed demography, in-hospital mortality, the extent of resection, the number of nodes resected, those affected by metastatic deposits and survival. The follow-up protocol consisted of 3-monthly consultant review for 2 years, followed by 6-monthly review thereafter to 5 years and then annually. When it was not possible for face-to-face review, information was obtained from the patient's primary physician. Further imaging was based on clinical grounds.

Data were analyzed with the method of Kaplan-Meier,[23] log-rank test, and Cox's proportional hazards regression for survival analysis.[24]

RESULTS

Two hundred twenty-four consecutive patients were identified from the database.



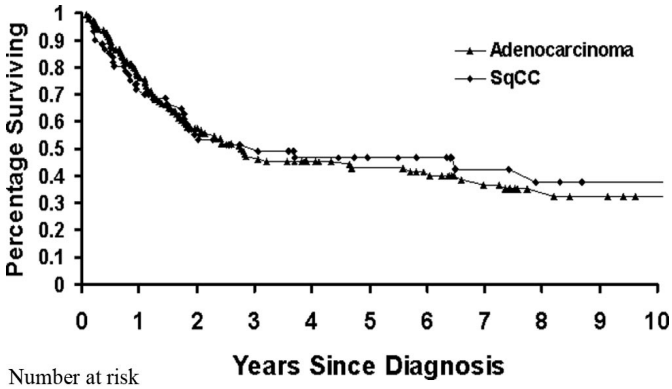
Number at risk

	0	1	2	3	4	5	6	7	8	9	10
Tis	11	10	9	7	6	5	4	3	3	3	3
Stage 1	37	35	29	25	23	19	16	13	8	6	5
Stage 2A	46	37	28	21	19	17	15	11	9	7	5
Stage 2B	34	27	17	13	7	5	3	1	1	1	1
Stage 3	74	44	21	11	8	7	6	3	3	3	3
Stage 4	14	3									

FIGURE 1. Patient survival according to AJCC (6th Edition) TNM staging.

There were 162 men (72%) with a median age of 65 years (range, 29–84 years). One hundred forty-eight patients (66%) had adenocarcinoma, 70 (31%) squamous cell carcinoma, and 6 (3%) were other tumor types (2 neuroendocrine tumors). Neoadjuvant therapy was given to 67 patients (30%). Of these, 13 with extensive squamous carcinoma were given concurrent 45 Gy radiotherapy. The median length of follow-up was 20 months (range, 1–174). One hundred eighty-four patients (82%) had been reviewed within the last 12 months (up to August 2008). The in-hospital mortality was 3.5%. A R0 resection was achieved in 88%, R1 (defined as tumor extending to the resection margin, including circumferential margin) in 10%, and R2 in 2%. The AJCC stage distribution was as follows: stage 0, $n = 11$ (5%); stage 1, $n = 38$ (17%); stage 2A, $n = 46$ (20%); stage 2B, $n = 37$ (16%); stage 3, $n = 78$ (35%); and stage 4, $n = 14$ (6%). Nodal disease was detected in 122 patients (54.4%). Overall 5-year survival as plotted by Kaplan-Meier analysis was 43%, with a median survival of 33.6 months (Figure 1). Patients with node-positive disease had a 5-year survival of 23% (median, 31 months). Locoregional recurrence occurred in 14% after a median of 11.5 months. There was also a significant relationship in survival between both the TNM stage of disease ($p < 0.001$; Figure 1) and increasing depth of tumor invasion ($p < 0.001$). However, there was no relationship between either histologic type of tumor (adenocarcinoma versus squamous cell; $p = 0.66$; Figure 2) and tumor site (mid, lower esophagus, and gastroesophageal junction; $p = 0.96$). There was no significant difference between patients who had undergone neoadjuvant therapy or surgery alone ($p = 0.98$; Figure 3). With multivariate analysis, independent predictors for diminished survival were male sex, age older than 75 years, and residual tumor.

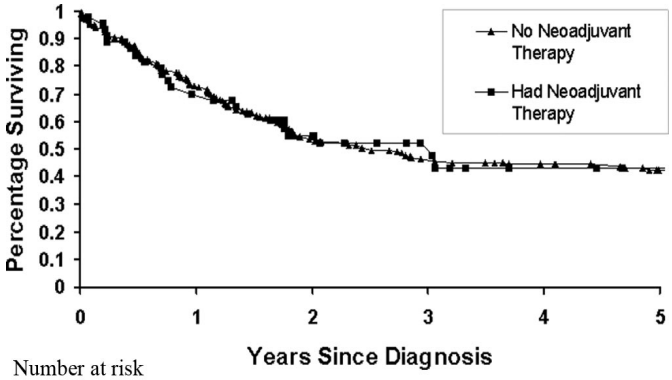
The median number of nodes resected in the specimens was 17 (range, 12–26). Analysis of the number of nodes affected by metastatic disease showed that there was a significant relationship between those having four or more nodes involved. Patients with less than four nodes involved had a median survival of 17.7 months, but four or more nodes



Number at risk

	0	1	2	3	4	5	6	7	8	9	10
Adenocarcinoma	148	108	75	59	49	48	36	28	18	16	13
Sq cell carcinoma	70	49	35	28	26	21	18	14	11	10	9

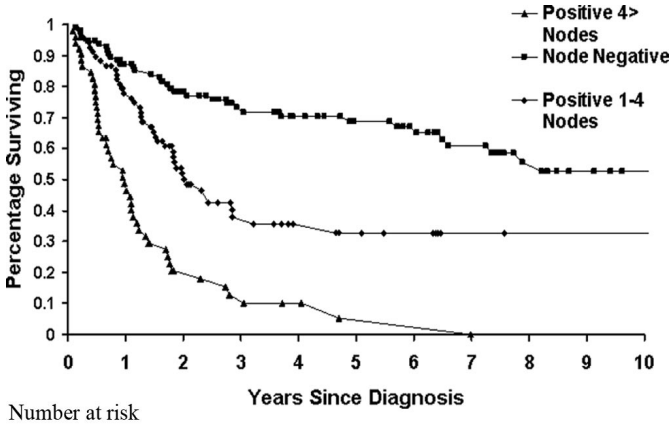
FIGURE 2. Overall survival in patients according to histologic subtype.



Number at risk

	0	1	2	3	4	5	6	7	8	9	10
Neoadjuvant therapy	44	30	20	10	7	6	5	3			2
Surgery alone	181	132	94	78	71	61	51	39	27	22	21

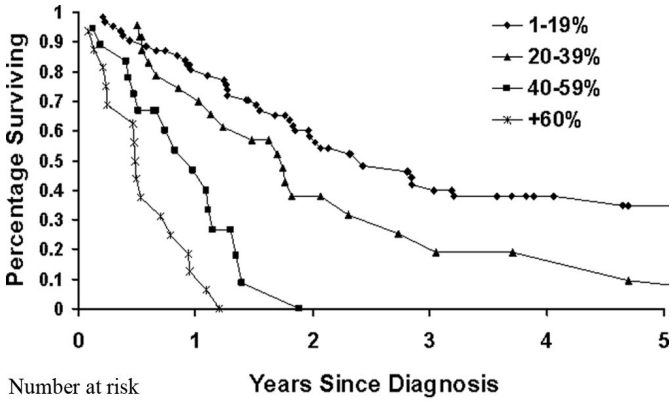
FIGURE 3. Survival according to the administration of neoadjuvant therapy versus surgery alone.



Number at risk

	0	1	2	3	4	5	6	7	8	9	10
<4	60	46	29	19	12	10					
≥4	60	28	9	5	3	1					

FIGURE 4. Survival according to absolute number of lymph node metastases resected.



Number at risk

	0	1	2	3	4	5	6	7	8	9	10
1-19%	62	48	31	20	13	10					
20-39%	24	17	9	4	2	1					
40-59%	18	7									
+60%	16	1									

FIGURE 5. Overall survival in patients stratified with increasing metastatic lymph node ratios.

involved gave a median survival of 9 months ($p < 0.001$; Figure 4). Further analysis of the ratio of nodes affected to the total number resected showed a significant decrease in survival as the percentage of positive nodes increased ($p < 0.001$; Figure 5). In patients who had less than 20% of nodes involved, median survival was 27.4 months, falling to 22 months for 20 to 40% of nodes affected, 12.8 months for 40 to 60% of nodes involved, and when more than 60% of resected nodes were affected, survival was a dismal 6.5 months.

DISCUSSION

It is well recognized that there is an adverse effect on survival when there are metastatic nodes after esophageal resection. However, the extent of LN resection remains controversial because some series have reported similar outcomes after minimal resection compared with those advocating dissections that are more extensive.[4] However, it remains a justifiable principle of cancer surgery, as demonstrated in other tumors, that more radical resections with LN clearance can confer a survival benefit.[25] It is based on this principle that en-bloc resection of the esophagus is more likely to achieve a real R0 resection by not leaving positive LNs, and so results are likely to be better after surgery. The level of local recurrence will also be improved (as in this series). Extensive resection with lymphadenectomy has shown improved survival in reported series with 5-year survival rates of 40 to 50%,[4,22] compared with a contemporary meta-analysis of 25%.[2]

The sixth TNM staging system only took account of whether regional LN metastases are present or not, and this was translated into a stage grouping. This created a problem, because there was no provision for the absolute number of nodes affected, which has been shown in several series to predict survival more accurately.[9–20] It also failed to measure the completeness of the lymphadenectomy. The general consensus of these studies is that four or more metastatic nodes is prognostic, and this is borne out in our series, because there

was a significant reduction in survival after surgery in patients who had four or more nodes affected. Based on this, the seventh revision of the TNM system to include subgroups of the N stage hopes to allow more accurate prediction of survival.

The sixth revision of the TNM classification states that a minimum number of six nodes should be sampled to allow classification of the nodal status.[7] This is low, particularly when it takes into account other sites, such as colon and stomach, which require 12 and 15 nodes, respectively. It should also be noted that these cancers also have different node groupings (N1-3). The seventh edition is less specific in the absolute number of nodes resected; however, it states that the degree of lymphadenectomy required is dependant on the T stage. In reality, this is unrealistic, because the staging is based purely on pathologic stage. It is difficult to justify the extent of surgery performed purely on clinical staging, because more extensive lymphadenectomy has been shown to provide a survival benefit,[22] and clinical staging is less accurate and so difficult to establish the "right" number and extent of nodal removal. It is simply necessary to be able to adequately remove LNs without excess morbidity and mortality.

A recent study by Bogoevski et al.[18] has examined whether the number of nodes resected should be higher. They suggested that a minimum number of 18 should be examined to allow accurate staging. In 255 patients who underwent oesophagectomy with curative intent, the numbers of nodes resected were stratified into three groups, less than 6, 6 to 18, and 19 and higher. This approach demonstrated that patients with either N0 or N1 disease with less than 19 nodes had similar survival rates. They concluded that it is probable that this could be explained by a degree of missed metastatic disease when fewer LNs are analyzed, as with low numbers there is a risk of sampling error (i.e., not finding metastatic nodes and grouping a patient as N0 when in fact the patient should be grouped as N1).

Bogoevski's group further reviewed the ratio of LNs with metastatic involvement. Groups were identified with ratios of less than 11%, 11 to 33%, and more than 33%. This demonstrated significantly improved survival in patients with lower ratios and was further borne out by the observation that there was little difference in patients staged as N0 with 18 or fewer nodes analyzed (median survival 36 months) and in patients with N1 disease but more than 18 nodes resected and a low ratio of affected nodes (median survival 28 months). They concluded that the current nodal staging classification was insufficient, and that LN ratios should be considered in substaging within the pN1 classification. In our series, the median LN yield was 17. Further analysis of node yield during two separate time periods, namely the first (1991–1998) and second (1999–2006) half of the series showed average yields of 13 and 20 nodes, respectively. However, this was not associated with any difference in survival between the two groups. There was no change of technique during the series, so this finding implies that the increased detection of nodes was due to improved pathologic reporting rather than being due to more radical surgery or experience of the surgeons.

Other series have examined the prognostic effect of involved node to total node ratios,[9,12,13,17,18–20] but they have only examined an arbitrary-defined cutoff point (between 0.1 and 0.3). Two recent studies have tried to stratify this further by using two cutoff points to stratify patients to three risk groups and have shown that there are further prognostic differences.[18,20] We have tried to be less arbitrary and to substratify the ratios more fully in our series. This has shown significant differences between four different groups with cutoff points of 0.2, 0.2 to 0.4, 0.4 to 0.6, and more than 0.6. We would suggest that this is a more sensitive analysis, particularly when there are significant differences between these groups. However, it is important to recognize that a systematic lymphadenectomy will remove more nodes and allow more accurate staging using this system because when the total number of nodes removed increases, it will likely drive down the ratios to a better prognostic group.

At the time of analyzing the data and constructing this article, the seventh edition was not in print, and hence this discussion was based on the previous classification (as is all the current evidence). The new classification now recognizes different nodal classification (N1–3) based on coarse groupings of the number of nodes involved. Although there is now recognition that increasing nodal involvement (and so tumor burden) is prognostic, there is still no requirement for assessment of the ratio of nodal metastases to total lymphadenectomy. Indeed, the manual states that the data do not support LN ratio; paradoxically, this article and others however do support this.[9–20] The main issue with LN ratio is that the denominator (i.e., the number of nodes sampled) is variable and that this can dilute the prognostic value. In this study, the number of nodes resected was higher (range, 12–26) than previously required, and the recommendation from the AJCC is that ideally 12 to 22 nodes should be sampled.

Previous editions of the TNM classification ignored histologic type, but the seventh edition specifically separates adenocarcinoma and squamous cell carcinoma and stages them differently. The data indicate that squamous cell carcinoma has a poorer prognosis, but this was not borne out in this series (and paradoxically this trend was reversed, albeit not significantly).

One of the weaknesses of the new staging classification is that it is based purely on pathologic data of patients who have undergone surgery alone. It is increasingly common for patients to receive neoadjuvant therapy because data show that this is of benefit in patients with operable esophageal cancer.[26] Because many studies report varying definitions of responses, the specific reason for this benefit is less clear; it may be due to downstaging of the primary tumor or from treatment of tumor cells that have already spread. Despite this reported benefit, our analysis did not show a significant difference between these groups.

Both the findings of no difference in overall survival based on the histologic type, or use of neoadjuvant therapy, adds further weight to the argument that it is the degree of

lymphadenectomy performed rather than the tumor site per se that is important.

We note that this cohort of patients were a heterogeneous group, with different tumor types resected. However, the same conclusions can be drawn, because the pattern of LN metastases for the tumor sites is similar. LN involvement is a significant prognostic indicator of overall survival and disease-free survival, and as the number of involved nodes increases, it may suggest a greater tumor burden or more aggressive tumor biology, and so the likelihood of locoregional or systemic recurrence could be assumed to be higher. However, this series shows that prognosis after surgery can be significantly affected by the ratio of affected nodes to the number of nodes resected after radical resection, and therefore stage grouping of the LN is not simply positive or negative. In an age when it is increasingly important to stage patients correctly to make decisions on adjuvant therapy, inclusion into clinical trials, and inform patients, this type of prognostic information is vital to both physicians and patients alike. This study demonstrates that the accuracy of the current TNM classification is suboptimal and that there should be revision of the nodal reporting, taking into account the ratio of involved nodes to the total number resected. Therefore, we propose oesophagectomy with radical en-bloc lymphadenectomy should become the standard of care, because it is apparent that survival is likely to be improved after surgery. It also provides optimal staging and is therefore a better prognostic indicator of survival than current conventional pathologic reporting.

REFERENCES

1. Devesa SS, Blot WJ, Fraumeni JF Jr. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998;83:2049–2053.
2. Jamieson GG, Mathew G, Ludemann R, et al. Postoperative mortality following oesophagectomy and problems in reporting its rate. *Br J Surg* 2004;91:943–947.
3. Rouvelas I, Zeng W, Lindblad M, et al. Survival after surgery for oesophageal cancer: a population-based study. *Lancet Oncol* 2005;6: 864–870.
4. Stein HJ, von Rahden BHA, Siewert JR. Survival after oesophagectomy for oesophageal cancer. *Langenbecks Arch Surg* 2005;4:280–285.
5. Stein HJ, Feith M, Bruecher BL, et al. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. *Ann Surg* 2005;242:566–573.
6. Tachibana M, Kinugasa S, Hirahara N, et al. Lymph node classification of esophageal squamous cell carcinoma and adenocarcinoma. *Eur J Cardiothorac Surg* 2008;34:427–431.
7. Sobin LH, Wittekind C (Eds.). TNM Classification of Malignant Tumours (UICC S.), 6th Ed. Hoboken, NJ: John Wiley & Sons Inc., 2002.
8. Greene FL, Page DL, Fleming ID (Eds.). AJCC Cancer Staging Manual, 6th Ed. New York, NY: Springer, 2002.
9. Roder JD, Busch R, Stein HJ, et al. Ratio of invaded to removed lymph nodes as a predictor of survival in squamous cell carcinoma of the oesophagus. *Br J Surg* 1994;81:410–413.
10. Ellis FH Jr, Heatley GJ, Krasna MJ, et al. Esophagogastrectomy for carcinoma of the esophagus and cardia: a comparison of findings and results after standard resection in three consecutive eight-year intervals with improved staging criteria. *J Thorac Cardiovasc Surg* 1997;113: 836–846.
11. Korst RJ, Rusch VW, Venkatraman E, et al. Proposed revision for the staging classification of esophageal cancer. *J Thorac Cardiovasc Surg* 1998;115:660–670.
12. Nigro JJ, DeMeester SR, Hagen JA, et al. Node status in transmural esophageal adenocarcinoma and outcome after en bloc esophagectomy. *J Thorac Cardiovasc Surg* 1999;117:960–968.
13. Hagen JA, DeMeester SR, Peters JH, et al. Curative resection for esophageal adenocarcinoma: analysis of 100 en bloc esophagectomies. *Ann Surg* 2001;234:520–530.
14. Rice TW, Blackstone EH, Rybicki LA, et al. Refining esophageal cancer staging. *J Thorac Cardiovasc Surg* 2003;125:1103–1113.
15. Bollschweiler E, Baldus SE, Schröder W, et al. Staging of esophageal carcinoma: length of tumor and number of involved regional lymph nodes. Are these independent prognostic factors? *J Surg Oncol* 2006; 94:355–363.
16. Rizk N, Venkatraman E, Park B, et al; American Joint Committee on Cancer staging system. The prognostic importance of the number of involved lymph nodes in esophageal cancer: implications for revisions of the American Joint Committee on Cancer staging system. *J Thorac Cardiovasc Surg* 2006;132:1374–1381.
17. Barbour AP, Rizk NP, Gonen M, et al. Lymphadenectomy for adenocarcinoma of the gastroesophageal junction (GEJ): impact of adequate staging on outcome. *Ann Surg Oncol* 2007;14:306–316.
18. Bogoevski D, Noken F, Koenig A, et al. Is it time for a new TNM classification in esophageal carcinoma? *Ann Surg* 2008;247:633–641.
19. Mariette C, Piessen G, Briez N, et al. The number of metastatic lymph nodes and the ratio between metastatic and examined lymph nodes are independent prognostic factors in esophageal cancer regardless of neoadjuvant chemoradiation or lymphadenectomy extent. *Ann Surg* 2008; 247:365–367.
20. Greenstein AJ, Litle VR, Swanson SJ, et al. Prognostic significance of the number of lymph node metastases in esophageal cancer. *J Am Coll Surg* 2008;206:239–246.
21. Edge SB, Byrd DR, Compton CC, et al. (Eds.). AJCC Cancer Staging Manual, 7th Ed. New York, NY: Springer, 2010.
22. Martin DJ, Church NG, Kennedy CW, et al. Does systematic 2-field lymphadenectomy for esophageal malignancy offer a survival advantage? Results from 178 consecutive patients. *Dis Esophagus* 2008;21: 612–618.
23. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
24. Cox D. Regression models and life tables (with discussion). *J R Stat Soc* 1972;187–220.
25. Pramesh CS, Kulkarni NN, Mistry RC, et al. Lymphadenectomy in cancer: time for a paradigm shift? *Lancet Oncol* 2006;7:450–451.
26. Gebski V, Burmeister B, Smithers BM, et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in esophageal carcinoma: a meta-analysis. *Lancet Oncol* 2007;8:226–234.

Diseases of the Esophagus (2008) **21**, 612–618
DOI: 10.1111/j.1442-2050.2008.00826.x

DISEASES OF THE ESOPHAGUS

Original article

Does systematic 2-field lymphadenectomy for esophageal malignancy offer a survival advantage? Results from 178 consecutive patients

D. J. Martin,[1,2] N. G. Church,[1] C. W. Kennedy,[2] G. L. Falk[1,2,3]

[1]*Concord Repatriation General Hospital,* [2]*Strathfield Private Hospital, and* [3]*Sydney Adventist Hospital, University of Sydney, Sydney, Australia*

SUMMARY. **More extensive resection for esophageal cancer has been reported to improve survival in several series. We compared results from an unselected consecutive cohort of patients undergoing radical esophagectomy, including removal of all periesophageal tissue with a 2-field abdominal and mediastinal lymphadenectomy for esophageal and gastroesophageal malignancy. A prospective electronic database was reviewed for patients with esophageal malignancy undergoing an open esophagectomy between 1991 and 2004. Data were analyzed on an SPSS file (version 12.0, Chicago, IL, USA) using χ^2 or Fisher's exact test; odds ratio and 95% confidence interval; and the Kaplan–Meier method, log–rank test and Cox's proportional hazards regression for survival analysis. There were 178 patients with a median age of 65 years and a 70/30 male to female ratio. Median follow-up was 20.4 months. Pathology comprised adenocarcinoma in 64% of patients, squamous cell carcinoma 30%, and other malignancies 6%. Seventeen patients had neoadjuvant therapy. Hospital mortality was 3.3%. Complete resection was achieved in 87%. Local recurrence occurred at a median of 13 months in 6.7% of patients. Overall 5-year survival was 42%. For patients with invasive squamous cell carcinoma and adenocarcinoma the 5-year survival was 47% and 40.3%, respectively, and for patients without nodal involvement it was 71.5%, with one to four nodes involved, 23.5% and with >4 nodes, 5% ($P < 0.001$). Survival decreased with increasing direct tumor spread ($P < 0.001$) and pathological stage ($P < 0.001$). Esophageal resection with systematic 2-field lymphadenectomy can be performed with acceptable operative mortality and favorable survival.**

KEY WORDS: **esophageal cancer, esophagectomy, lymphadenectomy, survival.**

INTRODUCTION

Survival after surgery for esophageal cancer has traditionally been poor. Jamieson described an in-hospital mortality of 8.8% and a 27.9% 5-year survival in a recent review of all published literature between 1990 and 2000.[1] Evidence for extended lymphadenectomy and extended lateral dissection is scant,[2–5] with only one randomized trial reporting a trend towards improved survival with a more extensive procedure.[6] Three Western series, utilizing two or three field dissections,[2,5,7] report perioperative mortality rates of 3–6.8%; comparatively low recurrence rates,[4] and 5-year survival rates of 40–52% supporting the possibility of a survival advantage from a more extensive surgical approach. This paper reports the postoperative mortality, locoregional recurrence and overall survival after esophagectomy with preservation of the pleura and pericardium, and removal of the subcarinal nodes and all mediastinal adventitia below the carina, and 2-field lymphadenectomy (2FL) in an unselected consecutive cohort of patients referred for surgery.

METHODS

A prospective database of consecutive esophagectomy patients was reviewed for demographic, hospital mortality, pathology, recurrence and survival data. All patients underwent a standardized surgical resection involving a mediastinal adventitial resection and a 2FL under the care of a single surgeon. Pathology was reported from three separate departments and all cases were staged using the American Joint

Address correspondence to: Assoc. Prof. Gregory L. Falk, 3 Everton Road, Strathfield, Sydney 2135, Australia. Email: gfalk@bigpond.net.au

Committee on Cancer (AJCC) criteria[8] from definitive operative histology.

Preoperative staging was performed by computerized tomography scan and selective endoscopic ultrasound. Bulky mid and lower esophageal lesions also underwent bronchoscopy and staging laparoscopy, respectively. All patients were offered surgery if the disease could be encompassed by resection, including when enlarged mediastinal, hepatic artery, celiac or splenic artery lymph nodes were apparent on preoperative assessment. Lesions primarily based in the gastric cardia, or Siewert III-type adenocarcinomas (AC), were treated by radical abdominal gastrectomy and hence not included in this series. Operative fitness was determined by clinical assessment, pulmonary function testing (forced expiratory volume in 1 second > 1l), arterial blood gas ($pO2 > 60$ mmHg) and cardiac imaging as clinically indicated. Surgery was performed by a modified Ivor-Lewis abdomino–thoracic (two-stage) technique or McKeown cervico–thoraco–abdominal (three-stage) technique as determined by the tumor site. Neoadjuvant therapy was used for tumors considered to be borderline resectable on preoperative imaging. Selected patients received postoperative chemotherapy if there was high predicted risk of recurrence.

Data were analyzed by SPSS (version 12.0, Chicago, IL, USA) using χ^2 or Fisher's exact test; odds ratio and 95% confidence interval (CI); and the Kaplan–Meier method, log–rank test and Cox's proportional hazards regression for survival analysis. Survival time was calculated from the date of surgery until death from any cause. Local tumor recurrence was defined as that occurring at the anastomosis or primary site of the tumor and regional recurrence as otherwise within the field of enbloc and lymph node clearance.

Data were compared in table form with those from contemporary large esophagectomy series (>100 patients) where either radical dissection with two or three field lymphadenectomy or more conventional techniques were described as the surgical method. Conventional techniques included either transhiatal esophagectomy or two- or three-stage resections without dedicated lymphadenectomy.

Surgical technique

The Ivor-Lewis-type procedure consisted of an open abdominal gastric mobilization and modified D2 gastric lymphadenectomy with splenic preservation followed by a right thoracotomy, lower and middle mediastinal adventitial resection with lymphadenectomy, and an intrathoracic anastomosis. The three-stage Mckeown procedure started with a similar thoracic dissection followed by open abdominal dissection and cervical anastomosis. Reconstruction was performed with a greater curve-based gastric conduit or when not available, an isoperistaltic colon.

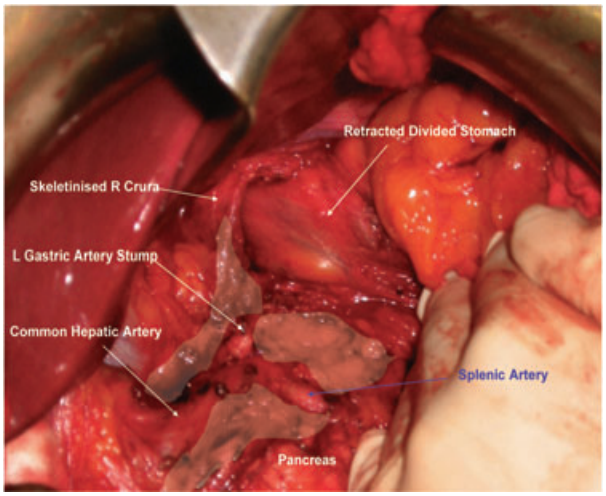


Fig. 1 Labeled clinical photograph: abdominal cavity post lymph node resection. Shaded areas represent nodal clearance around celiac trunk and its branches.

The abdominal procedure was performed through an upper midline laparotomy with construction of a gastric conduit based on right gastric and right gastroepiploic arterial pedicles. A Kocher's maneuver and pyloroplasty were routinely performed. The stomach was divided prior to ligation of the left gastric pedicle to facilitate exposure for lymph node dissection (Fig. 1). The nodal beds removed were equivalent to a gastric D2 lymphadenectomy, as defined and classified into numbered groups (LN) by the Japanese Gastric Cancer Association for a proximal gastric cancer with esophageal involvement with the exception of the splenic hilar nodes.[9] These included the nodal groups of the infradiaphragmatic hiatus and crura (LN 19 and 20); left gastric artery (LN 7); celiac trunk (LN 9); proximal and distal splenic artery (LN 11p and 11d); and the anterosuperior group of the common hepatic artery (LN 8a). D3 and M (metastatic) level lymph nodes along the hepatoduodenal ligament (LN 12) and proximal aorta (LN 16a1) were removed when clinically suspicious. Lower intrathoracic nodal groups (LN 110–112) were removed routinely as part of the thoracic component.

Thoracic dissection was performed with the patient in the lateral position through a right fourth or fifth intercostal posterolateral thoracotomy. The esophagus was resected on the mediastinum removing all periesophageal tissue, the thoracic duct, a segment of azygous vein, and diaphragmatic, periesophageal, subcarinal and bronchial nodes. The nodes immediately above the carina were removed with more proximal selective node removal in the upper third preserved for obvious nodes.

Table 1 Other malignancy

Patient	Pathology	AJCC TNM stage
1	Basaloid squamous carcinoma	3
2	Neuroendocrine carcinoma	2B
3	Small cell neuroendocrine carcinoma	2A
4	Leiomyosarcoma	2A†
5	Mixed SCC and small cell	2A
6	Adenosquamous Carcinoma	1
7	Mixed SCC, adenocarcinoma and neuroendocrine	2B
8	Adenosquamous carcinoma	3
9	Adenosquamous carcinoma	4B
10	Large cell with squamous differentiation	2B
11	Melanoma	2B

Overall 5-year survival for this group of patients was 20.8%. †Not classifiable by TNM with AJCC – tumor invaded muscularis propria. AJCC, American Joint Committee on Cancer; SCC, squamous cell carcinoma; TNM, tumor–node–metastasis.

RESULTS

One hundred seventy-eight patients were operated on between May 1991 and September 2004 with a median age of 65 years and male/female ratio of 70/30. Follow-up was achieved in 96.5% of cases, with a median of 20.4 months (0–4851 days). Resection was complete (R0) in 87%, microscopically incomplete (R1) in 10% and macroscopically (R2) in 3%. Tumor distribution was AC 64%, squamous cell carcinoma (SCC) 30% and other malignancies 6% (Table 1). The AJCC stage distribution was: stage 0, $n = 8$; stage 1, $n = 35$; stage 2A, $n = 36$; stage 2B, $n = 28$; stage 3, $n = 57$; and stage 4, $n = 14$. Nodal disease existed in 55.3% of patients. Neoadjuvant therapy was given in 17 patients with lesions of marginal resectability, (10 chemoradiation, six chemotherapy, one radiation) with clinical downstaging in six (35%). Postoperative adjuvant therapy was given in 13 patients with poor tumor or stage characteristics.

Surgical in-hospital mortality was 3.3%. Locoregional recurrence occurred in 22 patients (12.5%), of which 12 (6.7%) had local recurrence occurring at median of 13 months. (3–31 months). All but one have died of their disease during follow-up. Kaplan–Meier 5-year survival for the whole series was 42%, with *in situ* disease excluded 39% and for R0 resection 46%. Survival at 5 years for SCC was 47.4% (CI 32.3–61.0); AC 40.3% (CI 30.1–50.2); and other malignancy 20.8%. Survival decreased with increasing T (primary tumor) stage ($P < 0.001$) and AJCC pathological stage ($P < 0.001$) as seen in Figure 2. Survival in node negative patients ($n = 83$) was 71.5% at 5 years; with one to four positive nodes 23.4%; and more than four positive nodes 5% ($P < 0.001$) as shown in Figure 3. Multivariate analysis (after adjustment for patient age [<> 75 years] and tumor stage) revealed an independent association for diminished survival with male sex (HR2.0, CI 1.2–3.2); more than four positive nodes (HR2.2, CI 1.3–3.8); and residual tumor (HR1.8, CI 1.3–1.8). Bivariate analysis showed no difference in survival between tumors at the gastro-esophageal junction (GEJ) ($n = 66$) tumors and more proximal lesions ($n = 112$, $P = 0.96$).

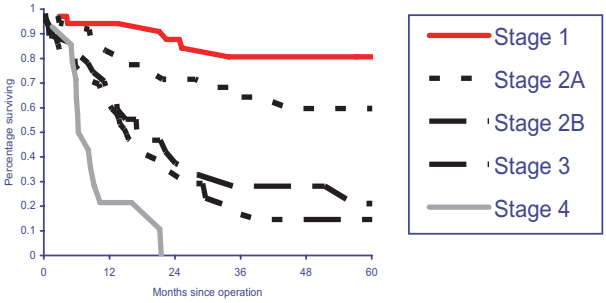


Fig. 2 Patient survival according to tumor American Joint Committee on Cancer tumor–node–metastasis status.

DISCUSSION

Conventional surgery for esophageal cancer over the last decade has produced 5-year survivals of 20–27% where as 'en bloc' and systematic lymphadenectomy series report 40–52% 5-year survival (Table 2).[2,5,7,10–16] Theoretical advantage of more radical resection includes more complete clearance of the primary tumor and both standard and microscopic lymph node metastases.

Hagen and colleagues[5] produced a 5-year survival rate of 52% in a series of 100 R0 resections for AC using a dissection similar to this series but involving the removal of the azygous vein and, in 62%, the spleen. The majority of patients also had a colonic conduit, facilitating the removal of much of the greater curve and omental nodes. Altorki and Skinner in a series of 111 patients undertook an aggressive approach that included removal of a cuff of diaphragm for tumors at the hiatus, routine removal of the anterior pericardium and, in 61 patients, a superior mediastinal and lower cervical

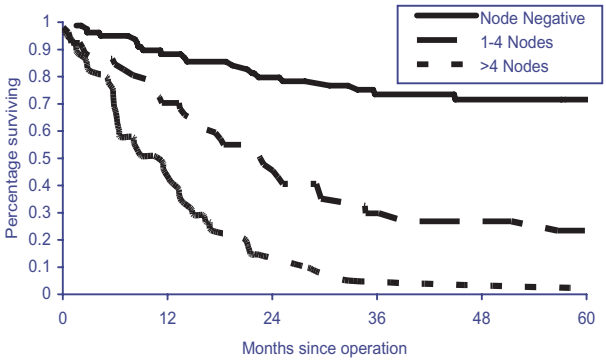


Fig. 3 Patient survival according to the number of lymph node metastases.

Table 2 Recent esophagectomy studies

Author	Year	*n*	Operation	Perioperative mortality rate (%)	Pathology adeno/SCC/ Other (%)	Staging distribution (%)						Survival % (5 years)
						(T)	Tis	1	3	3	4	
						(TNM)	0	1	2	3	3	
Conventional esophagectomy												
Zhang[16]	2005	121	TT	5	100/0/0	(T)	0	37	10	47	6	20
						(TNM)	0	35	24	35	6	
Orringer[10]	1999	800	TH	4.5	69/28/0	(T)			np			23
						(TNM)	9	12	34	37	8	
Vigneswarren[15]	1993	132	TH	2.3	77/23/0	(T)	4.5	14	20	57	4.5	21
						(TNM)	4	12	33	50	1	
Lieberman[12]	1995	258	TT	5	52/48/0	(T)	0	9	19	72	0	27†‡
						(TNM)			np			
Putman[11]	1994	221	TT/TH	6.8	66/33/0	(T)			np			19†
						(TNM)			np			
Gertsch[13]	1993	100	TH	3	57/43/0	(T)	0	6	18	40	36	23
						(TNM)			np			
Karl[14]	2000	143	TT	2.1	85/11/4	(T)			np			29 (3 years)
						(TNM)	10	13	38	31	8	
Systematic 2-field lymphadenectomy												
Martin	2005	178	TT	3.3	63/30/7	(T)	4	24	21	45	6	42
						(TNM)	4	20	36	32	8	
En bloc and extended lymphadenectomy												
Hagen[5]	2001	100	TT	6	100/0/0	(T)			np			52†§
						(TNM)	0	26	24	32	18	
Altorki[7]	2001	111	TT	6.8	63/27/0	(T)	0	22	19	56	3	40
						(TNM)	0	21	27	31	21	
Lerut[2]	2004	174	TT	3	54/46/0	(T)	1	14	14	70	1	42§
						(TNM)	1	9	28	29	34	

†Actuarial survival; ‡complete and microscopically incomplete resections included only; §complete resections included only – R0 rate 91%.
np, not published; SCC, squamous cell carcinoma; TNM, tumor–node–metastasis; T, tumor stage; TT, transthoracic; TH, transhiatal.

lymph node dissection along both recurrent laryngeal nerves, giving a 5-year survival of 40%.[7] The 5-year survival of 42% and 3.3% in-hospital mortality in our series using a systematic 2FL is not different from 'en bloc' series, with overall survival of 46% for complete resection.

Three field lymphadenectomy, advocated by many in Japan,[17,18] is also now being performed with some success in the West. Lerut[2] *et al.* have produced favorable survivals of 42% with a low 2.5% recurrent laryngeal nerve injury rate. The addition of the third field, although not appearing to benefit patients with gastroesophageal junction (GEJ) tumors, may offer improved survival for more proximal lesions.[2,19,20] Other experiences with this procedure however have reported significant morbidity and a decreased quality of life with respect to less radical esophagectomies.[21] The survival for the three-field dissection reported by Lerut is not different from the 2FL reported herein although there were more advanced lesions in the three-field cohort with a 25% difference in T3 lesions (Table 2).

The only randomized controlled trial (RCT) comparing a transthoracic (TT) radical dissection and transhiatal (TH) surgery in esophageal cancer, involving 220 patients all with AC, showed a trend towards improved 5-year survival favoring the TT procedure (39% vs 29%).[6] In this study from the University of Amsterdam the resection in the TT procedure was more extensive than our series, including the removal of the azygous vein and nodes of the aortopulmonary window. The TH procedure involved ligation of the left gastric artery at its base with further removal of D2 lymph nodes if clinically suspicious.

Earlier randomized studies[22,23] involving a total of 106 patients, all with SCC, found no significant difference in morbidity or survival between conventional TT and TH approaches. A further study of 26 patients,[24] which only ever published 1-year survival data, did not show a difference in outcome in comparing "en bloc" TT and "systematic lymphadenectomy" TH approaches. It did however demonstrate that lymph node retrieval was greater for the TT approach: 37.6 versus 19.9 nodes. This is consistent with cadaveric studies show the extensive TH approach does not achieve an equivalent lymphadenectomy to that done via thoracotomy.[25] A potential oncological advantage of a radical TT approach is that it allows routine removal of thoracic nodes, such as the supracarinal group that are not readily accessible from a TH approach.[24,25] Supracarinal nodes are involved in Barrett's related esophageal AC, in 4% and 16% of T2 and T3 lesions, respectively (Fig. 4).[26] More minimal disease may also be a factor with immunohistochemistry in esophageal and GEJ AC increasing nodal positivity, which has shown to be prognostic, by 33–60%.[27,28] The more radical TT arm of the large RCT from the University of Amster-

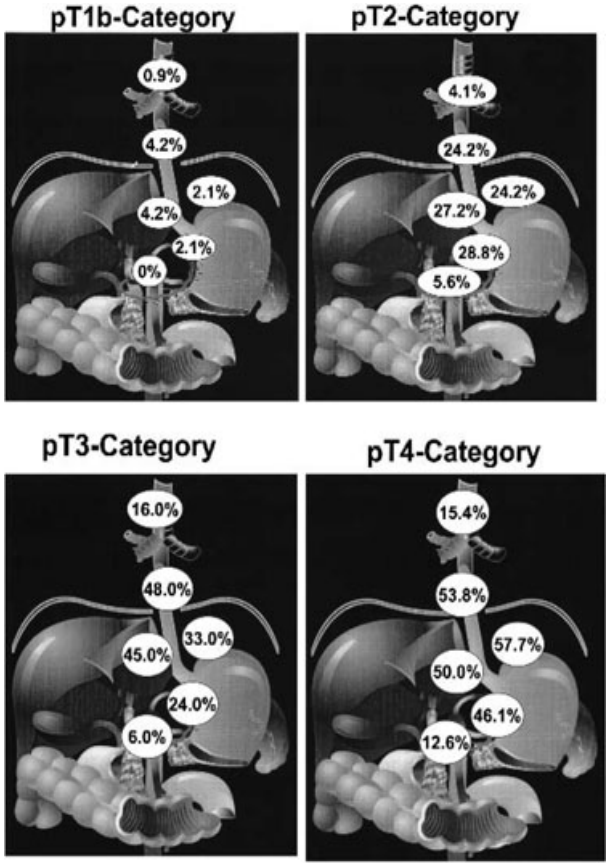


Fig. 4 Distribution of lymph nodes metastases with Barrett's cancer of the esophagus. The pattern of lymph node spread in adenocarcinomas of the distal esophagus is closely related to T-staging of the primary and occurs primarily in the paratumoral region of the lower posterior mediastinum, the paracardial region and along the lesser gastric curvature. A study of lymph node metastases in 286 cases of Barrett-type tumors with more than 15 nodes was sampled at esophagectomy (Reproduced from Feith M, Stein H J, Siewert J R,[26] with permission.)

dam study[6] had the same 5-year survival rate for AC as with our series, in comparison with the TH series listed in Table 2 with their subsequent less radical thoracic lymph node clearance.[10–16]

As the nodal drainage area of the lower esophagus (Fig. 4) includes cardiac gastric nodes, left gastric nodes and the celiac trunk, gastric D2 lymphadenectomy is theoretically appropriate to achieve R0 resection. Although there is little RCT evidence supporting the D2 procedure in gastric cancer, data from observational studies (including a Cochrane review) demonstrate that D2 resection for gastric cancer in specialist units is safe and achieves superior results.[29,30] The only two European RCT gastric lymphadenectomy trials have been confounded by the effect of high perioperative mortality of 10–13% of low volume surgeons.[31,32] In our series a 2FL, consisting of a modified gastric D2 lymphadenectomy with a mediastinal lymphadenectomy to above the level of the azygous, was achieved with mortality much less than that of the gastrectomy + D2 lymphadenectomy in these two trials. It appears therefore that experienced units can offer an abdominal lymphadenectomy safely and that this can be incorporated in techniques of esophageal resection with potential survival advantage.[2,3,6,7]

Various possibilities exist to explain the seeming improved figures of the 'en bloc' series. Patient sampling is one possibility, but as evident in Table 2, the T stage and tumor–node–metastasis (TNM) stage distribution is similar across the range of conventional and the other more radical series. Where published, we have included T-staging for comparison, which is less likely to be affected by upstaging with increased lymph node retrieval than the TNM system. The potential for upstaging however with the current AJCC N0 (node negative) or N1 (node positive) lymph node criteria is thus limited except when distal nodal involvement occurs as occurs in three field series. One hundred forty-one cases in our series were distal esophageal or GEJ carcinomas. AC tumors in this location are rapidly increasing in incidence and have a pattern of lymph node spread that is closely related to T-staging of the primary and occurs primarily in the paratumoral region (Fig. 4) of the lower posterior mediastinum, the paracardial region and along the lesser gastric curvature with skipped nodal stations reported in only 5% of cases.[26] Cervical lymphadenectomy however, as reported by Lerut, demonstrated further skipped nodal stations in 8% of patients, accounting for a large number of Stage 4 tumors in their results.[2]

Increased tumor clearance, with subsequent improved local control and longer survival, may be a factor. Dexter *et al.* found a clearance margin of 1 mm or less significantly decreased 3-year survival from 78% to 44% in patients with minimal nodal disease.[3] The R0 resection rate of 88% in our series may be in part due to the dissection on the mediastinum and subsequent increased pathological tumor clearance with respect to more minimalist techniques. The high proportion of distal tumors may also allow R0 resection due to the relative ease of clearance in the lower third. These factors may contribute to our series' relatively low local recurrence rate of 6.7% (locoregional 12%) at moderate follow-up of 20.4 months, compared with reported rates of local recurrence of 20–60% after standard surgical resection.[4]

In contemporary surgical practice it is also relevant as to whether this type of radical clearance can be applied to minimal invasive esophagectomy. It is our experience,[33] as well as that in large minimally invasive esophageal centers,[34] that although thoracoscopic and laparoscopic esophagectomy can be achieved with acceptable safety, completeness of tumor clearance and lymphadenectomy – especially in the thorax – does not yet match a radical open approach such as that described herein. Although it would be expected that a growing experience with laparoscopic radical abdominal lymphadenctomy for gastric cancer[35,36] would evolve to more aggressive

thoracoscopic clearance for esophageal cancer, the combined learning curves of both radical and minimally invasive techniques is unlikely to see this adopted nor achieved as a universal standard in the near future.

This series demonstrates that an 'en bloc' type of primary tumor excision for esophageal cancer and lymphadenectomy based on the known pattern of metastasis yields survival rates that are 10–20% better than contemporary and historical series, with acceptable mortality. Acknowledging the flaws in cohort comparison, the mechanism for this potential difference in survival remains uncertain, but may encompass more complete radial excision or lymphadenectomy. The operation performed in this series is less radical than the 'en bloc' operation reported by Skinner, Lerut and DeMeester, and has been applied unselectively. It has however yielded comparable results. Though randomized controlled trial evidence is lacking, the fact that this type of procedure can be performed without undue mortality in experienced hands would add support to the adoption of this technique as the contemporary surgical standard.

Acknowledgment

Dr Owen F. Dent for valuable statistical analysis and advice.

References

1 Jamieson G G, Mathew G, Ludemann R, Wayman J, Myers J C, Devitt P G. Postoperative mortality following oesophagectomy and problems in reporting its rate. Br J Surg 2004; 91: 943–7.
2 Lerut T, Nafteux P, Moons J *et al*. Three-field lymphadenectomy for carcinoma of the esophagus and gastroesophageal junction in 174 R0 resections: impact on staging, disease-free survival, and outcome: a plea for adaptation of TNM classification in upper-half esophageal carcinoma. Ann Surg 2004; 240: 962–72.
3 Dexter S P, Sue-Ling H, McMahon M J, Quirke P, Mapstone N, Martin I G. Circumferential resection margin involvement: an independent predictor of survival following surgery for oesophageal cancer. Gut 2001; 48: 667–70.
4 Altorki N K. The rationale for radical resection. Surg Oncol Clin N Am 1999; 8: 295–305.
5 Hagen J A, DeMeester S R, Peters J H, Chandrasoma P, DeMeester T R Curative resection for esophageal adenocarcinoma: analysis of 100 en bloc esophagectomies. Ann Surg 2001; 234: 520–30.
6 Hulscher J B, van Sandick J W, de Boer A G *et al*. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 2002; 347: 1662–9.
7 Altorki N, Skinner D. Should en bloc esophagectomy be the standard of care for esophageal carcinoma Ann Surg 2001; 234: 581–7.
8 Greene F L, Page D L, Fleming I D. *et al*., (eds). AJCC Cancer Staging Manual, 6th edn. New York, NY: Springer, 2002; 127–37.
9 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma – 2nd English edn. Gastric Cancer 1998; 1: 10–24.
10 Orringer M B, Marshall B, Iannettoni M D. Transhiatal esophagectomy: clinical experience and refinements. Ann Surg 1999; 230: 392–403.
11 Putnam J B, Suell D M, McMurtrey M J *et al*. Comparison of three techniques of esophagectomy within a residency training program. Ann Thorac Surg 1994; 57: 319–25.
12 Lieberman M D, Shriver C D, Bleckner S *et al*. Carcinoma of the esophagus. Prognostic significance of histologic type. J Thorac Cardiovasc Surg 1995; 109: 130–8.
13 Gertsch P, Vauthey J N, Lustenberger A A *et al*. Long-term results of transhiatal esophagectomy for esophageal carcinoma. A multivariate analysis of prognostic factors. Cancer 1993; 72: 2312–9.
14 Karl R C, Schreiber R, Boulware D *et al*. Factors affecting morbidity, mortality, and survival in patients undergoing Ivor-Lewis esophagogastrectomy. Ann Surg 2000; 231: 635–43.
15 Vigneswaran W T, Trastek V F, Pairolero P C, Deschamps C, Daly R C, Allen M S. Transhiatal esophagectomy for carcinoma of the esophagus. Ann Thorac Surg 1993; 56: 838–44.
16 Zhang X, Watson D I, Jamieson G G, Lally C, Bessell J R, Devitt P G. Outcome of oesophagectomy for adenocarcinoma of the oesophagus and oesophagogastric junction. Anz J Surg 2005; 75: 513–9.
17 Isono K, Sato H, Nakayama K. Results of a nationwide study on the three-field lymph node dissection of esophageal cancer. Oncology 1991; 48: 411–29.
18 Noguchi T, Wada S, Takeno S, Hashimoto T, Moriyama H, Uchida Y. Two-step three-field lymph node dissection is beneficial for thoracic esophageal carcinoma. Dis Esophagus 2004; 17: 27–31.
19 Tabira Y, Okuma T, Kondo K, Kitamura N J. Indications for three-field dissection followed by esophagectomy for advanced carcinoma of the thoracic esophagus. Thorac Cardiovasc Surg 1999; 117: 239–45.
20 Fujita H, Kakegawa T, Yamana H *et al*. Mortality and morbidity rates, postoperative course, quality of life, and prognosis after extended radical lymphadenectomy for esophageal cancer. Comparison of three-field lymphadenectomy with two-field lymphadenectomy. Ann Surg 1995; 222: 654–62.
21 Baba M, Aikou T, Natsugoe S *et al*. Quality of life following esophagectomy with three-field lymphadenectomy for carcinoma, focusing on its relationship to vocal cord palsy. Dis Esophagus 1998; 11: 28–34.
22 Goldminc M, Maddern G, Le Prise E, Meunier B, Campion J P, Launois B. Oesophagectomy by a transhiatal approach or thoracotomy: a prospective randomized trial. Br J Surg 1993; 80: 367–70.
23 Chu K M, Law S Y, Fok M, Wong J. A prospective randomized comparison of transhiatal and transthoracic resection for lower-third esophageal carcinoma. Am J Surg 1997; 174: 320–4.
24 Jacobi C A, Zieren H U, Muller J M, Pichlamaier H. Systematic lymphadenectomy in esophageal carcinoma – preliminary results of a prospective randomized study Zentralbl Chir 1996; 121: 110–5.
25 Herbella F A, Del Grande J C, Colleoni R. Efficacy of mediastinal lymphadenectomy in transhiatal esophagectomy with and without diaphragm opening: a cadaveric study. Dis Esophagus 2002; 15: 160–2.
26 Feith M, Stein H J, Siewert J R. Pattern of lymphatic spread of Barrett's cancer. World J Surg 2003; 27: 1052–7.
27 Waterman T A, Hagen J A, Peters J H, DeMeester S R, Taylor C R, Demeester T R. The prognostic importance of immunohistochemically detected node metastases in resected esophageal adenocarcinoma. Ann Thorac Surg 2004; 78: 1161–9.
28 Bonavina L, Ferrero S, Midolo V, Buffa R, Cesana B, Peracchia A J. Lymph node micrometastases in patients with adenocarcinoma of the esophagogastric junction. Gastrointest Surg 1999; 3: 468–76.
29 McCulloch P, Nita M E, Kazi H, Gama-Rodrigues J. Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach. [Systematic Review] Cochrane Database Syst Rev 2004; 3 AN: 00075320–100000000
30 Degiuli M, Sasako M, Calgaro M *et al*. (Italian Gastric Cancer Study Group). Morbidity and mortality after D1 and D2 gastrectomy for cancer: interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial. Eur J Surg Oncol 2004; 30: 303–8.

The authors have no conflicting interests to declare.

31 Bonenkamp J J, Hermans J, Sasako M, van de Velde C J. Extended lymph-node dissection for gastric cancer. Dutch Gastric Cancer Group. N Engl J Med 1999; 340: 908–14.
32 Cuschieri A, Weeden S, Fielding J *et al*. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer 1999; 79: 1522–30.
33 Martin D J, Bessell J R, Chew A, Watson D I. Thoracoscopic and laparoscopic esophagectomy: initial experience and outcomes. Surg Endosc 2005; 19: 1597–601.
34 Smithers B M, Gotley D C, Martin I, Thomas J M. Comparison of the outcomes between open and minimally invasive esophagectomy. Ann Surg 2007; 245: 232–40.
35 Huscher C G, Mingoli A, Sgarzini G *et al*. Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-year results of a randomized prospective trial. Ann Surg 2005; 241: 232–7.
36 Noshiro H, Nagai E, Shimizu S, Uchiyama A, Tanaka M. Laparoscopically assisted distal gastrectomy with standard radical lymph node dissection for gastric cancer. Surg Endosc 2005; 19: 1592–6.

Excerpta Medica

The American Journal of Surgery®

The American Journal of Surgery 185 (2003) 232–238
Scientic paper

Pathology of Barrett's esophagus by proton magnetic resonance spectroscopy and a statistical classication strategy

Sinead T. Doran, B.Sc.[a], Greg L. Falk[c], Ray L. Somorjai, Ph.D.[d], Cynthia L. Lean, Ph.D.[a], Uwe Himmelreich, Ph.D.[a], Jeanette Philips[b], Peter Russell[a], Brion Dolenko, M.Sc.[d], Alexander E. Nikulin, Ph.D.[d], Carolyn E. Mountford, D.Phil.[a,*]

[a]*Institute for Magnetic Resonance Research and Department of Magnetic Resonance in Medicine, University of Sydney, P.O. Box 148, St. Leonards, New South Wales 1590, Australia*
[b]*Department of Anatomical Pathology, Royal North Shore Hospital, St. Leonards, New South Wales 2065, Australia*
[c]*Stratheld Private Hospital, 3 Everton Rd., Stratheld, New South Wales 2135, Australia*
[d]*Institute for Biodiagnostics, National Research Council of Canada, Winnipeg, Manitoba R3B 1Y6, Canada*

Manuscript received December 21, 2001; revised manuscript August 17, 2002

Abstract

Background: Barrett's esophagus is thought to be a precursor of adenocarcinoma. The incidence of adenocarcinoma of the lower esophagus in the Western world is rising and accounts for more than 40% of esophageal carcinomas in males. It is not possible to identify which Barrett's patients are at high risk of developing malignancy. Here we applied a statistical classication strategy to the analysis of magnetic resonance spectroscopy and histopathological data from esophageal biopsies to ascertain whether this risk could be identied in Barrett's patients.
Methods: Tissue specimens from 72 patients (29 noncancer-bearing and 43 cancer-bearing) were analyzed by one-dimensional proton magnetic resonance spectroscopy at 8.5 Tesla. Diagnostic correlation was performed between the magnetic resonance spectra and histopathology. The magnetic resonance magnitude spectra were preprocessed, followed by identication of optimal spectral regions, and were then classied by cross-validated linear discriminant analysis of rank orders of the rst derivative of magnetic resonance spectra.
Results: Magnetic resonance spectroscopy combined with a statistical classication strategy analysis distinguished normal esophagus from adenocarcinoma and Barrett's epithelium with an accuracy of 100%. Barrett's epithelium and adenocarcinoma were distinguished with an accuracy of 98.6% but only when 4 of the Barrett's specimens and 7 of the carcinoma specimens, determined to be "fuzzy" (ie, unable to be accurately assigned to either class) were withdrawn. The 7 cancer and 4 Barrett's specimens, determined to be "fuzzy" using the Barrett's versus cancer (B versus C) classier, were submitted to the other two classiers (Barrett's versus normal [B versus N] and normal versus cancer [N versus C], respectively). The 4 Barrett's specimens were assigned to Barrett's by the N versus B classier and to normal ($n = 2$) or cancer ($n = 2$) classes by the N versus C classifer. The 7 cancer specimens were crisply assigned to the cancer class (N versus C), or for the B versus N classier, to the Barrett's class (ie, more similar to Barrett's than to normal tissue). Visual inspection of the spectra from histologically identied Barrett's epithelium showed a gradation from normal to carcinoma.
Conclusions: Proton magnetic resonance spectroscopy of esophageal biopsies combined with a statistical classication strategy data analysis provides a robust diagnosis with a high degree of accuracy for discriminating normal epithelium from esophageal adenocarcinoma and Barrett's esophagus. Different spectral categories of Barrett's epithelium were identied both by visual inspection and by statistical classication strategy, possibly reecting the risk of future malignant transformation.

Keywords: Barrett's epithelium; Esophagus; Pathology; Magnetic resonance spectroscopy; Adenocarcinoma; Mathematical statistical analysis

The incidence of adenocarcinoma of the lower esophagus in the Western world has risen 10% per year since the mid 1970s and currently accounts for more than 40% of esophageal carcinomas in men [1]. Barrett's disease, in which the normal stratied squamous epithelium of the lower esophagus is replaced by specialized columnar metaplastic epithelium, is thought to be a precursor to adenocarcinoma of the lower esophagus, increasing 40- to 50-fold [2] the risk of developing malignancy.

Studies of clinical outcomes have long suggested that the

* Corresponding author. Tel.: +612-9926-6073; fax: +612-9926-6549.
E-mail address: caro@imrr.usyd.edu.au

0002-9610/03/$ – see front matter
doi:10.1016/S0002-9610(02)01374-0

morphological and architectural features observed by light microscopy to diagnose disease processes have speci c, though circumscribed, de ciencies [3]. This is particularly true for early stages in tissue injury such as Barrett's esophagus, for which the outcome for a patient with early disease is uncertain [4].

Whereas histopathology can accurately distinguish normal epithelium from invasive carcinoma, accurate prediction of the behavior of potentially premalignant Barrett's epithelium is not possible [4]. A reliable and objective technique is clearly needed to identify Barrett's patients at high risk of developing adenocarcinoma, for whom ablation of the mucosa would be indicated.

The role of surveillance of patients with Barrett's epithelium is contentious [5]. The concept that an adenoma-carcinoma sequence, as documented for colon [6], may exist in the development of Barrett's epithelium has resulted in widespread endoscopy for the prevention of esophageal adenocarcinoma [5]. However, the existence of an adenoma-carcinoma sequence in the evolution of lower esophageal adenocarcinoma clearly needs to be substantiated.

Magnetic resonance spectroscopy is a relatively new technology capable of determining the pathology of human tissues [7–14]. It can also identify some stages in pathological processes before they are morphologically apparent, ie, able to be visualized by light microscopy [8,9,14]. It was demonstrated previously that one-dimensional proton magnetic resonance spectroscopy on esophageal tissue identi es chemical differences among normal epithelium, Barrett's epithelium, and adenocarcinoma [14]. These differences were identi ed by visual inspection of a limited number of magnetic resonance spectral regions. Quantifying the differences in these discrete frequencies as a function of the tissue histopathology did not provide a high level of diagnostic accuracy when large numbers of tissue specimens were included in the study.

Here we combine the proton magnetic resonance spectroscopy data with a robust statistical classi cation strategy that allows the entire magnetic resonance spectrum to be assessed objectively. The robustness of the statistical classi cation strategy methodology has been con rmed by the analysis of magnetic resonance spectra from thyroid [15], ovarian [16], prostate [10], breast [12], and brain [17] tissues. In the case of breast disease, the statistical classi cation strategy combined with magnetic resonance spectroscopy determines not only the pathology of the primary lesion but also whether axillary lymph nodes are involved, based on alterations to chemical species in the primary tumor alone [12]. (For a review of the statistical classi cation strategy, see Lean et al [18].)

Here, we consider the combined use of magnetic resonance spectroscopy and a statistical classi cation strategy to provide an objective diagnostic method that may aid in predicting the behavior of Barrett's epithelium, and therefore be useful for investigating the existence of tissue with a predisposition or commitment to malignancy in the lower esophagus.

Material and methods

All pathological and magnetic resonance spectroscopy analyses were undertaken in a blinded study. Correlation of the magnetic resonance spectroscopy data with clinicopathological criteria were was performed after all reports were led.

Patients and specimen collection

Tissue specimens were obtained from 72 patients, 29 noncancer-bearing and 43 cancer-bearing. Specimens were obtained by endoscopy for Barrett's epithelium, or esophagectomy for adenocarcinoma of the esophagus. Patients treated by chemotherapy, radiotherapy, or laser therapy were excluded. Endoscopy was performed under intravenous sedation using a Pentax or Olympus gastroscope with routine forceps. The endoscopic position and diagnosis were recorded. From patients undergoing endoscopy, mucosal biopsies from macroscopically normal (strati ed squamous) esophageal epithelium and Barrett's epithelium were obtained. For patients undergoing gastroesophagectomy for adenocarcinoma of the lower esophagus (Barrett's epithelium con rmed on preoperative biopsy), mucosal biopsies from macroscopically normal esophageal epithelium, Barrett's epithelium, and esophageal adenocarcinoma were obtained. All specimens were collected for both proton magnetic resonance spectroscopy analysis and correlative histopathology.

Specimen storage and preparation for magnetic resonance spectroscopy

All tissue specimens were placed in polypropylene vials containing 300 μL phosphate-buffered saline in deuterated water (PBS/D_2O). Vials were immediately snap-frozen in liquid nitrogen and stored at -70°C for up to 6 weeks until magnetic resonance spectroscopy assessment. Prior to the magnetic resonance spectroscopy experiment each specimen was thawed, washed three times in PBS/D_2O, and transferred to a 5-mm magnetic resonance spectroscopy tube containing 400 μL PBS/D_2O. Postmagnetic resonance spectroscopy specimens were xed in 10% neutral buffered formalin for histopathology analysis.

Magnetic resonance spectroscopy

One-dimensional proton magnetic resonance spectroscopy experiments were carried out at 37°C on a Bruker Avance 360 wide-bore spectrometer (Bruker Biospin, Rheuistetten, Germany) operating at 360.1 MHz (8.5 Tesla), and equipped with a standard 5-mm [^{1}H, ^{13}C] probehead.

The sample was spun at 20 Hz. Residual water signal was suppressed by selective gated irradiation. Spectra were acquired as previously described [9] over a sweep width of 3,600 Hz (10 ppm) using a 90° pulse, 8K data points, 256 accumulations, an acquisition time of 1.14 s, and a relaxation delay of 2 s.

Magnetic resonance data were prepared for the statistical classi cation strategy–based analysis, using the in-house software XPREP (Institute for Biodiagnostics, National Research Council, Winnipeg, Manitoba). Magnitude spectra consisting of 4096 data points over the spectral width of 10 ppm, were reduced to 1,500 points between 0.35 and 4.0 ppm. Magnetic resonance spectra were normalized to the total integral in this region. Rank-order of the rst derivative of magnetic resonance spectra was used for the statistical classi cation strategy analysis.

Histopathology

All specimens, including those already assessed by magnetic resonance spectroscopy from both endoscopies and gastroesophagectomies, were xed in 10% neutral buffered formalin, paraf n embedded, sectioned at 5 μm, and stained with hematoxylin and eosin according to standard protocols for histopathological assessment. Tissue preservation, relative proportions of mucosa to submucosa, type of metaplasia, degree of dysplasia, and presence of in ammatory cells were reported in addition to the diagnosis.

Statistical classi cation strategy

A three-stage statistical classi cation strategy [18,19] was designed speci cally for magnetic resonance and infrared spectra of bio uids and tissue biopsies, for which typical datasets bases contain many fewer spectra than number of data points (attributes) in each spectrum. The strategy consists of three stages; however, in some cases only the rst two stages are required. First, the data points of the magnetic resonance magnitude spectra are preprocessed (in order to eliminate redundant information and noise) by submitting them to a Genetic Algorithm-based Optimal Region Selection (GA_ORS) procedure [20], which nds a few (at most 5 to 10) maximally discriminatory subregions in the spectra. The averages in these subregions are the ultimate features, and are used at the second stage.

The second stage uses the features found by GA_ORS to develop linear discriminant analysis (LDA) classi ers that are made robust by an in-house (Institute for Biodiagnostics, National Research Council, Winnipeg, Manitoba) bootstrap-based crossvalidation method [21]. The crossvalidation approach proceeds by randomly selecting about half the spectra from each class and using these to train a classi er (LDA). The resulting classi er was is then used to validate the remaining half. This process is repeated 1000 times (with random replacement), and the optimized LDA coef cients are saved. The ultimate classi er is the weighted average of the 1,000 different bootstrap classi er coef cient sets and is designed to be used in a clinical setting as the single best classi er. The classi er yields probabilities of class assignment for the individual spectra.

For particularly dif cult classi cation problems, the third stage is activated. This aggregates the outputs (class probabilities) of two or more independent classi ers to form a computerized consensus diagnosis [15,17]. The consequence of computerized consensus diagnosis is that classi cation accuracy and reliability are generally better than for the best of the individual classi ers. Note that the accuracies presented are calculated only after removing those spectra that are classi ed unreliably, ie, as "fuzzy" classi cations.

Results

Typical proton magnetic resonance spectra from histologically normal esophageal epithelium and adenocarcinoma of the esophagus are shown in Fig. 1,A and D, respectively. Spectra from Barrett's epithelium from a non-cancer-bearing patient and Barrett's epithelium from a cancer-bearing patient are shown in Fig. 1, B and C, respectively. Resonances previously assigned in the spectra include those from the methyl (CH_3) and methylene (CH_2) protons of lipid at 0.9 ppm and 1.3 ppm, respectively, and from the N-trimethyl [$+N(CH_3)_3$] of choline and choline-based metabolites at 3.2 ppm [14]. Additional resonances include those from acyl chain protons (-CH=CH-CH_2-) and N- or O-acetyl groups at 2.0 ppm; creatine (Cr) and lysine (Lys) at 3.0 ppm; taurine (Tau) at 3.4 ppm; protons of carbohydrate residues (CHOH) in the 3.58 to 4.02 ppm region [14].

The rst two stages of the statistical classi cation strategy–based analysis were applied to the three major histological categories, ie, normal esophageal tissue, Barrett's epithelium, and esophageal adenocarcinoma. Three pair classi ers were developed: normal versus carcinoma (N versus C), normal versus Barretts's (N versus B), and Barrett's versus carcinoma (B versus C). The results are listed in Table 1.

The combination of the statistical classi cation strategy and magnetic resonance spectroscopy distinguished normal esophageal tissue from adenocarcinoma with 100% sensitivity and speci city. The overall crispness of the data classi cation using the N versus C classi er was 98.3%, ie, 1 of 64 samples was determined to be "fuzzy" (a concise term we used to indicate that the probability of belonging to either class is less than 75%). An overall 100% accuracy was obtained when the fuzzy specimen was excluded.

Using a separate classi er, N versus B, Barrett's tissues were distinguished from normal esophagus again with 100% sensitivity and speci city. The overall crispness of the data was 98.4%, ie, 1 of 70 samples was determined to be fuzzy. An overall 100% accuracy was obtained when the fuzzy specimen was excluded.

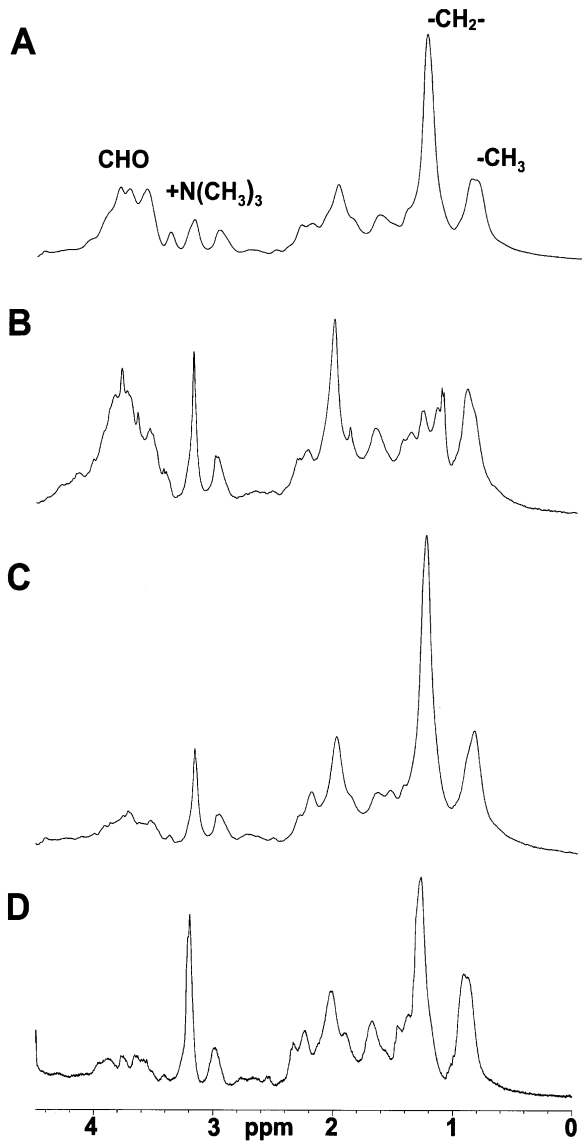


Fig. 1. One-dimensional proton magnetic resonance spectra (8.5 Tesla) of esophageal biopsies from four different histopathological subtypes: (A) normal esophagus, (B) Barrett's epithelium from noncancer-bearing patients, (C) Barrett's epithelium from cancer-bearing patients, and (D) adenocarcinoma.

A third classi er was developed to distinguish Barrett's epithelium (known from clinical outcomes to be sometimes destined for malignancy or already malignant) from esophageal adenocarcinoma (B versus C). The two pathologies were distinguished with a sensitivity and speci city of 97.3% and 100%, respectively. The overall crispness of the data was low, however, at 84%. Here the statistical classi cation strategy determined 11 of 41 specimens to be fuzzy. When the 11 "fuzzy" specimens (7 cancers, 4 Barrett's) were excluded, an overall 98.6% accuracy was obtained.

The 11 specimens determined to be fuzzy using the B versus C classi er were reclassi ed using the other two classi ers, ie, N versus C and N versus B. The N versus C classi er crisply assigned the 7 cancers to the cancer class. The four Barrett's specimens were assigned to the normal class (n = 2, fuzzy) and to the cancer class (n = 2, crisp). When submitted to the N versus B classi er, 6 of the 7 cancers were crisply assigned to the Barrett's class, ie, classifed as closer in chemical signature to Barrett's than to normal esophagus. One cancer remained fuzzy. The 4 Barrett's samples were crisply assigned to the Barrett's class.

In the development of each pair classi er, speci c spectral regions were identi ed as optimal for discriminating the two classes. Three one-dimensional spectral regions were found to distinguish normal esophageal tissue from carcinoma. These were 0.92 to 1.12 ppm, 3.23 to 3.28 ppm, and 3.49 to 3.57 ppm. Three spectral regions, ie, 1.37 to 1.43 ppm, 1.93 to 2.06 ppm, and 3.50 to 3.54 ppm, were also required to distinguish normal esophageal tissue from Barrett's esophagus. Four spectral regions, ie, 1.21 to 1.29 ppm, 1.45 to 1.49 ppm, 2.51 to 2.57 ppm, and 3.05 to 3.13 ppm, were required to distinguish Barrett's esophagus from esophageal carcinoma.

Visual inspection of the magnetic resonance spectra allows the distinction between normal and cancer to be made. Spectra from Barrett's epithelium showed a gradation between normal and malignant. Representative magnetic resonance spectra of Barrett's epithelium from cancer and noncancer-bearing patients are shown in Fig. 2, A and B, respectively. These two types of tissue are histologically indistinguishable and yet the magnetic resonance spectra are distinct. Spectra from malignant tissue or Barrett's have an increased choline (3.2 ppm) to creatine (3.0 ppm) ratio compared with normal esophagus. A relative decrease in the carbohydrate region at 3.5 to 4.0 ppm (compared with the creatine-containing metabolites at 3.0 ppm) distinguishes cancer and Barrett's (cancer-bearing patients) from normal tissue and Barrett's (noncancer-bearing patients).

Comments

Proton magnetic resonance spectroscopy monitors biochemical changes that continue to occur throughout tumor development and progression [22,23]. This study has demonstrated that the proton magnetic resonance pro le of Barrett's epithelium from cancer and noncancer-bearing patients is different from that of normal esophagus and esophageal adenocarcinoma. Furthermore, and most importantly, Barrett's epithelia that are histologically indistinguishable were divided on the basis of visual inspection of the magnetic resonance spectroscopy pro les into two categories (Fig. 2). In support of the magnetic resonance spectroscopy diagnosis is the observation that one category of Barrett's epithelium originated from patients with adenocarcinoma elsewhere in the esophagus, ie, not identi ed by histopathology in the tissue biopsy examined by magnetic resonance spectroscopy.

The two-stage statistical classi cation strategy–based analysis of the magnetic resonance spectroscopy data, including preprocessing of the raw magnetic resonance spectra and subsequent computerized classi cation, effectively allows all data points in each spectrum to be examined.

Table 1
Statistical classi cation strategy analysis of magnetic resonance spectra from normal esophagus, Barrett's epithelium, and esophageal adenocarcinoma

	Sensitivity (%)	Speci city (%)	Percent crisp	Fuzzy	Accuracy	Misclassi ed	Spectral regions used
Normal (n = 29) versus carcinoma (n = 35)	100	100	98.3	1	100	0	3.49–3.57 ppm; 3.23–3.28 ppm; 0.92–1.12 ppm
Normal (n = 29) versus Barrett's (n = 41)	100	100	98.4	1	100	0	3.50–3.54 ppm; 1.93–2.06 ppm; 1.37–1.43 ppm
Barrett's (n = 41) versus carcinoma (n = 35)	97.3	100	84.1	11	98.6	1	3.05–3.13 ppm; 2.51–2.57 ppm; 1.45–1.49 ppm; 1.21–1.29 ppm

There was no need to invoke the third stage for this data set. It was thus possible to distinguish between normal and malignant esophageal tissue, and between normal esophagus and Barrett's epithelium, with 100% accuracy. For each of these two pair classi ers only one sample in each data set was "fuzzy," ie, unable to be assigned unambiguously to a class, and no samples were misclassi ed. Barrett's epithelium was also distinguished from esophageal adenocarcinoma with a high degree of accuracy, but only when 11 "fuzzy" samples were removed from the data set. The assignment of the 4 "fuzzy" Barrett's spectra to the normal class by the other two classi ers suggests that different chemical pro les exist in the Barrett's category. The 7 cancers initially found to be "fuzzy" were con rmed by the N versus C classi er to be cancer and were assigned to the Barrett's class, ie, closer to Barrett's than to normal tissue, by the N versus B classi er.

There was overlap between the spectral regions, selected by GA_ORS, used to develop the respective classi ers. That suggests that many metabolites may have contributed to the success of the statistical classi cation strategy–based methodology. It was not possible to identify particular metabolites of key diagnostic importance, as most regions identify frequency ranges that may include a large number of chemical species.

There is substantial histopathological evidence supporting the existence of an adenoma-carcinoma sequence in the esophagus. Evidence includes the histological demonstration of varying grades of dysplasia in the same Barrett's epithelium segment, the presence of Barrett's epithelium adjacent to adenocarcinoma, and the presence of adenocarcinoma in resected specimens of high-grade dysplasia in as many as 50% of cases of Barrett's epithelium [24]. Other evidence includes the over- expression of p53 in adenocarcinoma and dysplasia in Barrett's epithelium [25], a variation of between 7% and 88% in the extent of point mutations in the p53 gene in patients with Barrett's epithelium

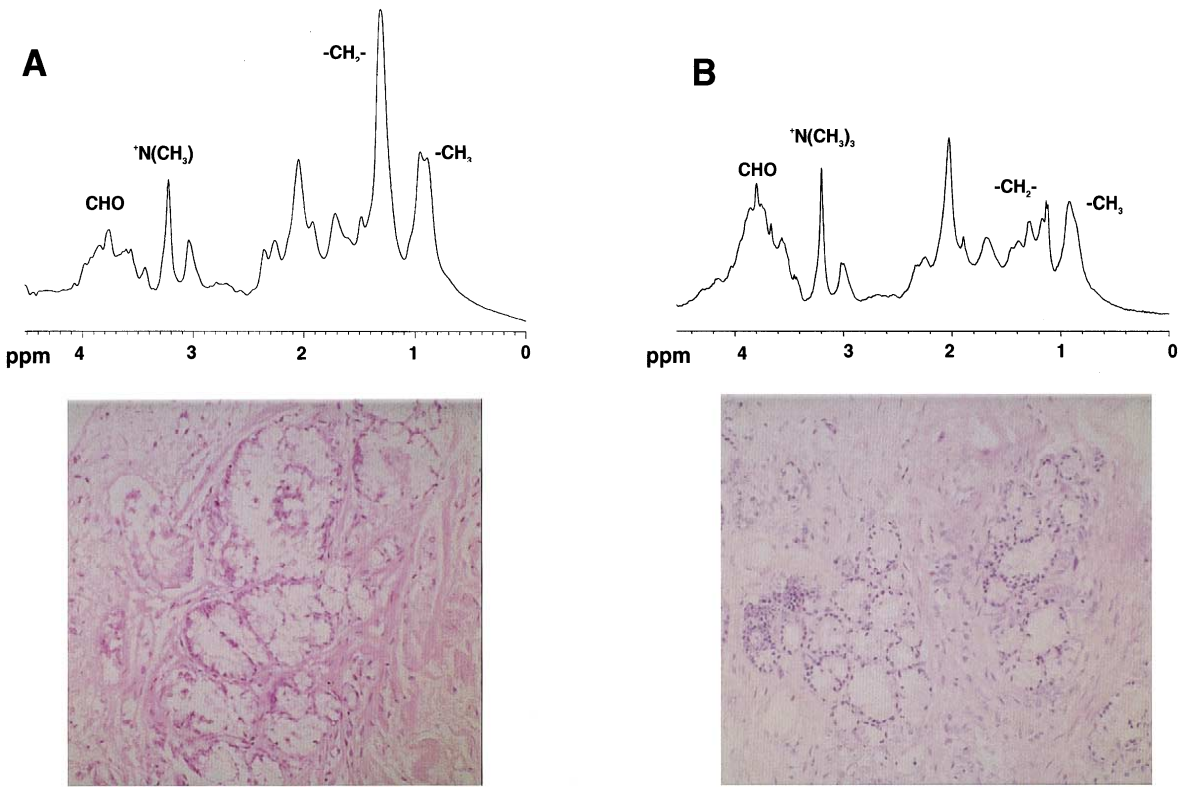


Fig. 2. One-dimensional proton magnetic resonance spectra (8.5 Tesla) of Barrett's epithelium from (A) cancer-bearing patients and (B) noncancer-bearing patients with the corresponding histopathology. (Hematoxylin and eosin, ×200.)

[26], 17p and 5q allelic loss in adenocarcinoma and high-grade dysplasia in Barrett's epithelium [27], and the observation that aneuploidy occurs frequently in adenocarcinoma and high-grade dysplasia in Barrett's epithelium and is not present in specialized intestinal metaplasia [28].

Visual inspection of the magnetic resonance spectra from tissues categorized histologically as Barrett's epithelium showed a gradation between normal and adenonomacarcinoma. Interestingly, those specimens from patients with cancer elsewhere in the esophagus had spectra more similar to an adenocarcinoma spectrum on visual inspection. These ndings are consistent with previous ndings for magnetic resonance spectroscopy analysis of follicular adenoma of the thyroid, where histologically similar specimens were found by magnetic resonance spectroscopy and magnetic resonance chemical shift imaging to be different [8,9,29]. Larger numbers of specimens of Barrett's epithelium now need to be examined by magnetic resonance spectroscopy to determine if there is indeed an adenoma-carcinoma sequence present or if indeed the spectral differences are the result of a eld change [30] in this disease process.

A major challenge in the management of Barrett's epithelium is the extent of surveillance of patients with dysplasia. Magnetic resonance spectroscopy has potential diagnostic value in the identi cation of high- and low-risk mucosa, enabling targeted surveillance. The ability to identify Barrett's epithelium destined for adenocarcinoma prior to histological manifestation would be highly effective for triaging patients for surveillance and treatment. The potential for curative resection of earlier diagnosed adenocarcinoma of the esophagus may enhance long-term survival. Identi cation of a magnetic resonance spectroscopy signal indicative of the presence of high-grade dyplasia or adenocarcinoma elsewhere in the esophagus may allow earlier diagnosis of unrecognised tumors elsewhere.

Conclusions

A two-stage statistical classi cation strategy–based analysis of proton magnetic resonance spectral data from esophageal biopsies provided a robust classi cation-based diagnosis with a high degree of accuracy for normal epithelium, Barrett's esophagus, and adenocarcinoma. Visual inspection of the magnetic resonance spectra identi ed a gradation in the Barrett's category, possibly re ecting the risk of future malignant transformation in this histologically indeterminate category.

Acknowledgments

Supported by Australian NH&MRC 991155. Carolyn Mountford and Peter Russell acknowledge major share holdings in Sydney Magnetic Resonance Foundation.

References

[1] Blot WJ, Devesa SS, Kneller RW, Fraumeni JF. Rising incidence of adenocarcinoma of the oesophagus and gastric cardia. JAMA 1991; 265:1287–9.

[2] Clark GW, Smyrk TC, Burdiles P, et al. Is Barrett's metaplasia the source of adenocarcinomas of the cardia? Arch Surg 1994;129:609–14.

[3] Rambo ON. The limitations of histologic diagnosis. Prog Radiat Ther 1962;2:215–22.

[4] Spechler SJ. Barrett's oesophagus. Semin Gastroeintest Dis 1996;7: 51–60.

[5] Spechler SJ, Goyal RK. Cancer surveillance in Barrett's esophagus: what is the end point? Gastroenterology 1994;106:275–6.

[6] Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61:759–67.

[7] Delikatny EJ, Russell P, Hunter JC, et al. Proton MR and human cervical neoplasia: ex-vivo spectroscopy allows distinction of invasive carcinoma of the cervix from carcinoma in-situ and other preinvasive lesions. Radiology 1993;188:791–6.

[8] Lean CL, Delbridge L, Russell P, et al. Diagnosis of follicular thyroid lesions by proton magnetic resonance on ne needle biopsy. J Clin Endocrinol Metab 1995;80:1306–11.

[9] Russell P, Lean CL, Delbridge L, et al. Proton magnetic resonance and human thyroid neoplasia. I: discrimination between benign and malignant neoplasms. Am J Med 1994;96:383–8.

[10] Hahn P, Smith IC, Leboldus L, et al. The classi cation of benign and malignant human prostate tissue by multivariate analysis of proton magnetic resonance spectra. Cancer Res 1997;57:3398–401.

[11] Rutter A, Hugenholtz H, Saunders JK, Smith IC. Classi cation of brain tumors by ex vivo ^{1}H NMR spectroscopy. J Neurochem 1995; 64:1655–61.

[12] Mountford CE, Somorjai RL, Malycha P, et al. Diagnosis and prognosis of breast cancer by magnetic resonance spectroscopy of ne needle aspirates analyzed using a statistical classi cation strategy. Br J Surg 2001;88:1234–40.

[13] Mackinnon WB, Barry P, Malycha P, et al. Fine-needle biopsy specimens of benign breast lesions distinguished from invasive cancer ex vivo with proton MR spectroscopy. Radiology 1997;204: 661–6.

[14] Barry P, Wadstrom C, Falk G, et al. What is the value of 1H MRS in detecting early malignant changes?. In: Giuli R, editor. The oesophagogastric junction. Montrouge: John Libbey Eurotext, 1998, p 1122–7.

[15] Somorjai RL, Nikulin SE, Pizzi N, et al. Computerized consensus diagnosis: a classi cation strategy for the robust analysis of MR spectra. I. Application to ^{1}H spectra of thyroid neoplasms. Magnet Reson Med 1995;33:257–63.

[16] Wallace JC, Raaphorst GP, Somorjai RL, et al. Classi cation of ^{1}H MR spectra of biopsies from untreated and recurrent ovarian cancer using linear discriminant analysis. Magnet Res Med 1997;38:569–76.

[17] Somorjai RL, Dolenko B, Nikulin AK, et al. Classi cation of proton MR spectra of human brain biopsies: the in uence of preprocessing and computerized consensus diagnosis on classi cation accuracy. J Magnet Res Imag 1996;6:437–44.

[18] Lean CL, Somorjai RL, Smith ICP, et al. Accurate diagnosis and prognosis of human cancers by proton MRS and a three-stage classi cation strategy. In: Webb G, editor. Annual reports NMR Spectros. New York: Academic Press, 2002;48:71–111.

[19] Somorjai RL, Dolenko B, Nikulin A, et al. Distinguishing normal from rejecting renal allografts: application of a three-stage classi - cation strategy to MR and IR spectra of urine. Vib Spectros 2002; 28:97–102.

[20] Nikulin AE, Dolenko B, Bezabeh T, Somorjai RL. Near-optimal region selection for feature space reduction: novel preprocessing methods for classifying MR spectra. NMR Biomed 1998;11:209–17.

[21] Efron B, Tibshirani RJ. An introduction to the bootstrap. Monographs of statistics and applied probability. Vol 57. New York: Chapman Hall, 1993.

[22] Lean C, Mackinnon WB, Delikatny EJ, et al. Cell surface fucosylation and magnetic resonance spectroscopy characterization of human malignant colorectal cells. Biochemistry 1992;31:11095–105.

[23] Mackinnon WB, Huschtscha L, Dent K, et al. Correlation of cellular differentiation in human colorectal carcinoma and adenoma cell lines with metabolite pro les determined by ^{1}H magnetic resonance spectroscopy. Int J Cancer 1994;59:248–61.

[24] Streitz JM, Andrews CW, Ellis FH. Endoscopic surveillance of Barrett's esophagus. Does it help? J Thorac Cardiovasc Surg 1993;105: 383–7.

[25] Ireland AP, Clark GW, DeMeester TR. Barrett's oesophagus: the signi cance of p53 in clinical practice. Ann Surg 1997;225:17–30.

[26] Wang Y, You M, Reynolds SH, et al. Mutational activation of the cellular Harvey ras oncogene in rat esophageal papillomas induced by methyl benzylnitrosamine. Cancer Res 1990;50:1591–5.

[27] Blount PL, Meltzer SJ, Yin J, et al. Clonal ordering of 17p and 5q allelic loss in Barrett's dysplasia and adenocarcinoma. Proc Natl Acad Sci USA 1993;90:3221–5.

[28] Reid BJ, Haggitt RC, Rubin CE, Rabinovitch PS. Barrett's esophagus. Correlation between ow cytometry and histology in detection of patients at risk for adenocarcinoma. Gastroenterology 1987;93:1–11.

[29] Rutter A, Kunnecke B, Dowd S, et al. Proton magnetic resonance and human thyroid neoplasia. III. Ex vivo chemical-shift microimaging. J Magnet Res 1996;110:240–8.

[30] Polacarz SV, Darne J, Sheridan EG, et al. Endocervical carcinoma and precursor lesions: c-myc expression and the demonstration of eld changes. J Clin Path 1991;44:896–9.

Diseases of the Esophagus (2001) **14,** 17–22

DISEASES OF THE ESOPHAGUS

Original article

Adenocarcinoma of the rat esophagus in the presence of a proton pump inhibitor: a pilot study

K. H. Moore,[1] P. Barry,[1] J. Burn,[2] G. Falk[3]

[1]Department of Surgery, University of Sydney; [2]Davies, Campbell de Lambert Pathology, Rhodes; [3]Department of Surgery, Concord Hospital, Sydney, NSW, Australia

SUMMARY. **This study examines the effects of a proton pump inhibitor on a rat model of duodenogastric reflux. Duodenoesophageal reflux was induced in 60 rats by performing a duodenesophagostomy. The study group received daily intraperitoneal injections of a proton pump inhibitor for 6 months and the control group received an equivalent injection of saline. Rats were examined at death for macroscopic tumor, dysplasia, adenocystic changes, papillomatosis, and adenocarcinoma. Five out of 19 rats in the study group and three out of 20 rats in the control group developed dysplastic/adenocarcinomatous changes. Ten of the rats in the study group died before the end of the study, as opposed to one in the control group (this is not statistically significant). There was no difference in the number of cancers that developed in the two groups. However, there was an insignificant trend to earlier appearance of detectable disease in the study group.**

INTRODUCTION

Columnar-lined esophageal mucosa associated with esophagitis, as first described by Norman Barrett,[1] occurs in approximately 10–12% of patients investigated for gastroesophageal reflux disease.[2,3] Persistent exposure to gastric juices is responsible for the changes that result in Barrett's metaplasia,[4–8] and it as been proposed that dysplasia and adenocarcinoma may occur as a result of exposure to duodenogastric reflux.[4,9–13] It is generally accepted that adenocarcinomas arising in Barrett's mucosa display sequential development and progression, from normal Barrett's epithelium to dysplasia, carcinoma in situ and, ultimately, to invasive adenocarcinoma.[14,15] It is less common for adenocarcinomas of the esophagus or esophagogastric junction to arise in the absence of Barrett's disease or intestinal metaplasia.[14–21]

The incidence of adenocarcinoma in the lower esophagus and cardioesophageal junction is increasing. In some regions it now accounts for 40% of esophageal malignancies.[22–29] The reason for this rise is unknown.

Address correspondence to: Dr G. Falk, PO Box 1085, Strathfield NSW 2135, Australia. Tel: (+61) 297 451099; Fax: (+61) 297 451299; E-mail: glf@tpg.com.au

The use of proton pump inhibitors for the treatment of gastroesophageal reflux has increased over the last two decades. Despite extensive investigation and clinical use of antacids, these agents have not been examined in patients with Barrett's esophagus or in an animal model simulating duodenogastric reflux. This study examines the potential role of proton pump inhibitors in patients with duodenoesophageal reflux, using Sprague–Dawley rats as a model.

MATERIALS AND METHODS

Sixty male, 8-week-old Sprague–Dawley rats, *Rattus norvegicus* (150–250 g), were used as models for adenocarcinoma of the esophagus, as described previously by Atwood[30] and Pera.[31] Each rat underwent a laparotomy and side-to-side duodenoesophagostomy under gaseous anesthesia. The proximal duodenum was mobilized and an enterotomy was made in the duodenum 1 cm distal to the pylorus. A full-thickness longitudinal incision in the lower esophagus was made down to, but not including, the gastroesophageal junction. An anastomosis was performed using a single-layer continuous 7/0 polydioxanone suture under the operating microscope (Fig. 1). This anastomosis allowed duodenal juice to mix with gastric contents and alkalinize the stomach,

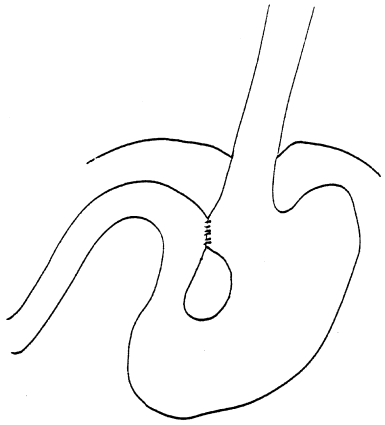


Fig. 1 Gastroduodenal anastomosis.

simulating duodenoesophageal reflux. The skin was then closed using a 4–0 polypropylene suture.

Pre- and postoperatively the rats had access to water, but otherwise were fasted for 12 h. An intraoperative dose of ampicillin was administered. All rats were then housed in standard laboratory animal accommodation with two rats to a cage.

The rats were randomized into two groups of 30. The first group received a daily intraperitoneal injection of the proton pump inhibitor, omeprazole, at a dose already proven to raise plasma gastrin levels and induce achlorhydria in rats.[32,33] The second group were given equivalent injections of saline daily. The injections commenced 2 months postoperatively and continued for 6 months.

The rats were examined daily for signs of disease and weighed weekly. Any rats that exhibited disease or weight loss of greater than 15% of initial body weight over the 6-month period were killed using carbon dioxide. Rats exhibiting behavior consistent with pain or discomfort or a general failure to thrive (as determined by an independent observer) were also killed. The surviving rats were all killed 6 months after the commencement of injections.

The eosophagus and stomach of each rat was dissected en bloc, fixed in 10% buffered formalin and sent to histopathology. A pathologist who was blinded to the study examined the specimens for macroscopic tumor, dysplasia, adenocystic changes of papillomatosis, and adenocarcinoma.

The incidence of dysplastic/adenocarcinomatous changes was compared between the two groups using chi-squared tests and survival functions were analyzed using the Kaplan–Meier method and Cox regression.[34,35]

RESULTS

Twenty-one rats died perioperatively. Twenty of the remaining 39 were control rats, and 19 were from the group receiving omeprazole. Table 1 describes the pathologic findings from both groups.

In the control group, all except one rat survived for 6 months. In the study group, 10 rats were killed prior to 6 months as they were in poor health, losing weight, or failing to thrive. Eight of these 10 showed abnormal histopathology and five had dysplastic/adenomatous changes.

Overall, eight (21%) rats (three from the control group and five from the study group) developed dysplasia or adenocarcinoma. The survival curves of these eight rats were compared and showed that there was an insignificant trend to earlier detection of disease in the group of rats given omeprazole (Fig. 2).

DISCUSSION

Recently, studies have examined the role of refluxate in carcinogenesis of the esophagus, in particular the role of certain components: bile/pancreatic juices and nitrosamines. Mirvish and Rosinsky demonstrated that in rats squamous cell carcinomas of the esophagus can be induced by certain nitrosamines.[36] Attwood *et al.* subsequently induced carcinomas of the esophagus using nitrosamines in rat models with different reflux mechanisms. They found that there was a 7% increase in adenocarcinoma in those rats who had duodenal reflux alone and a 35% increase in those that had duodenal reflux and were administered nitrosamines. The group with only gastric reflux did not show an increase of carcinoma above that of the non-refluxing control animals.[30] It was concluded that duodenal reflux plays a role as a promoter in the development of adenocarcinoma.

Other studies have shown increases in squamous cell carcinomas in models with gastroduodenal

Table 1. Pathologic findings of control and study group

Pathology	Control group (saline) ($n=20$)	Omeprazole group (PPI) ($n=19$)
Normal	14	11
Inflammatory changes	3	1
Barrett's esophagus	–	2
Dysplasia	–	2
Adenocarcinoma	–	–
Adenocarcinoma in Barrett's	3	3

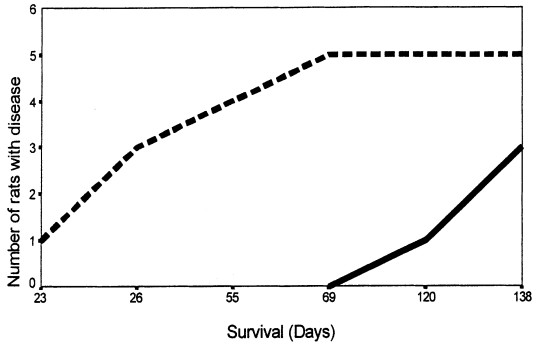


Fig. 2 Trends in survival of rats with dysplasia or adenocarcinoma. Omeprazole group, – – –; control group, ——.

reflux.[31,37] The differentiation from squamous cell to adenocarcinoma is thought to be dependent upon the duodenal secretions present rather than the gastric components of the reflux. Subsequently, Pera *et al.* have shown that the pancreatic juices initiate carcinogenic change while bile salts act as co-carcinogens.[38]

Although duodenogastric reflux has been shown to promote adenocarcinomas of the lower esophagus in animal models, as outlined above, there are few studies that give evidence of the relationship in man. 'Alkaline reflux' has been identified in patients with dysplastic Barrett's epithelium,[8,39] indicating the possible presence of pancreaticobiliary constituents in this patient group and congruous with the genesis of columnar-lined epithelium in animals.[30,38] Yasui *et al.* found excess duodenal reflux in patients with gastric carcinoma but did not examine esophageal carcinomas.[40] With the advent of a fiberoptic probe for the measurement of bilirubin, the presence of increased esophageal duodenal juices has been confirmed in patients with Barrett's epithelium.[41] Further data are required before a direct relationship between duodenal refluxate and esophageal adenocarcinomas can be verified in man.

Results of animal studies suggest that duodenal juices have a carcinogenic effect on the stomach, small intestine, and colon.[42–46] These studies have been supported by human studies that have reported an increased incidence of elevated bile salts in patients with gastric and colonic carcinomas.[47,48] It is interesting to note that there is also a higher rate of colonic polyps associated with complicated Barrett's esophagus. This may be related to the carcinogenic effects of bile salts.[49,50]

It is unknown how duodenal juices actually act upon the esophageal mucosa, but it has been hypothesized that components may directly affect cell proliferation and DNA indexes.[51] Bile acids have been shown to cause esophageal injury *in vitro*, but they are difficult to assay and have only recently been measured in gastric aspirates of humans. Subsequently, it was proven that bile acids are neutralized and inactivated in the gastric pH environment.[52] In an achlorhydric environment, bile acids are not neutralized and are potentially capable of refluxing in an 'active' state. Acid suppression may therefore increase the concentration of 'active' bile salts and promote epithelial injury or carcinogenesis. Pancreatic juices have also been implicated as having a direct carcinogenic effect.[53]

Helicobacter is important in the pathogenesis of gastric carcinoma; however, its role in the development of Barrett's esophagus and its complications is uncertain. There have been several recent publications that demonstrate an inverse relationship between the presence of *Helicobacter pylori* and dysplastic changes within Barrett's esophagus.[54–56]

With regard to the carcinogenesis of gastric neoplasia, it was proposed by Correa that duodenal reflux acts indirectly by changing the acidity of the stomach and allowing overgrowth of nitrosamine-producing bacteria.[57] This theory correlates with the observed increased incidence of gastric carcinoma in patients who have had antrectomy for ulcer disease,[58–60] in achlorhydric patients[61] and, potentially, in patients with severe duodenal reflux. In these situations, there is an alteration in the pH of the stomach. Ruddell *et al.*[62] has shown that an increase in gastric pH and subsequent bacterial overgrowth results in a rise in gastric nitrite, which can be metabolized to *n*-nitroso compounds. There is a positive association between gastric cancer and the concentration of nitrite in gastric juices.[63,64]

Direct measurement of nitrosamines has been difficult to date. This has resulted in some controversy regarding the mutagenic nature of nitrosamines and raises some questions about the validity of the Correa hypothesis. Walters *et al.* demonstrated that, in the presence of bacterial overgrowth and at a neutral pH, nitrosamines are in a greater concentration.[65] The method of assay used has been criticized for a lack of sensitivity. The method of Bavin *et al.*, which lacks specificity, in contrast, finds that nitrosamines are at a greater concentration in an acid pH environment.[66] Using slightly different methods, Sobala *et al.* also produced evidence that does not support the Correa hypothesis.[67] While the debate on the actual concentration of the mutagenic nitrosamines continues, individual components have not been assayed to date. It may be variations in the concentrations of individual *n*-nitroso compounds that determine mutagenicity and not the overall quantity of nitrosamines. However, the positive relationship between gastric cancer and nitrite concentration is not in doubt.[63,64]

A rise in antral pH or achlorhydria will result in a rise in gastrin levels and cause antral G-cell hyperplasia.[68,69] In *in vitro* experiments, gastrin has been shown to promote the growth of both normal gastrointestinal epithelium[70] and tumors.[71–76] Increased gastrin levels have also been found in patients with colorectal cancer.[77] A recent study by Karakai *et al.* showed that squamous cell carcinomas grow more rapidly under the influence of high levels of gastrin, but that there was no differentiation to the adenocarcinomas.[78] Jankowski *et al.* identified epidermal growth factor receptors in Barrett's esophagus and it may be that gastrin or other components of duodenal reflux act at similar receptor sites to induce carcinogenesis.[39]

Potent acid suppression has been shown to result in prolonged fourfold increases in basal gastrin measures in man.[79] It is therefore possible that elevated levels of gastrin secondary to potent acid suppression may potentiate growth and intestinal

metaplasia in Barrett's epithelium. Long-term studies on drug-induced hypochlorhydria and the development of cancer have been undertaken and no increased significant risk could be detected in gastric carcinomas. However, these studies did not report the occurrence of esophageal carcinomas.[80–82]

Existing data support an association between duodenal reflux, achlorhydria, nitrosamine concentration and Barrett's esophagus, and the development of adenocarcinoma of the esophagus.

Most proton pump inhibitor studies have been carried out using omeprazole, a selective competitive inhibitor of the H^+,K^+-ATPase in parietal cell canuliculi.[83] Initially, omeprazole is widely distributed but is later confined to the parietal cells, in which it becomes protonated and is unable to pass back across the cell membrane. It is then converted to its active form and binds with the ATPase, irreversibly inactivating the enzyme.[84]

Omeprazole effectively blocks basal and stimulated gastric acid secretion, decreasing it by 70%.[85] As a result, bacterial flora is altered, there is an increase in nitrites and moderate hypergastrinemia can result with long-term use.[86,87] In animal studies, gastric enterochromaffin cell hyperplasia and carcinoid tumors developed in a dose-related fashion with omeprazole. It was thought to be related to hypergastrinemia and a subsequent trophic effect.[88–93] However, this was not reproduced in humans.[94–97] Other toxicity studies on animals and short-term follow-up studies of patients using omeprazole have not found an association between adenocarcinoma of the esophagus and treatment.[98] Omeprazole has been shown to heal esophagitis and remove the inflammatory stimulus to cell damage and replication.[99] The balance of the effects of the decreased inflammation with proton pump inhibitors and the theoretical basis of potential cancer prevention is unknown in animals or humans.

In conclusion, the importance of this study is the attempt to assess the balance of risks in a reflux model hitherto not performed. This pilot study indicated that there was no significant difference in the development of dysplasia or adenocarcinoma between rats that had omeprazole treatment and rats that did not, although an insignificant trend toward earlier detection was seen in the treatment arm. The model demonstrated a basal rate of dysplastic/carcinomatous degeneration of 21% and confirms its value in assessing promotion or inhibition of reflux-related carcinoma.

Acknowledgments

The authors would like to thank Mr G. Dew and Mr G. Fox of Autosuture, Australia, and Dr Jun Hong Sun of the Liver Transplant Laboratory.

References

1. Barrett N. The description of columnar lined esophagus associated with esophageal reflux. Br J Surg 1958; 131: 58–64.
2. Bremner C G. The columnar-lined (Barrett's) esophagus. In: Nyhus L M, ed. Surgery Annual, Vol. 9. New York: Appleton-Century-Crofts, 1977: 103–123.
3. Winters C Jr, Spurling T J, Chobanian S J. *et al*. Barrett's esophagus. A prevalent, occult complication of gastroesophageal reflux disease. Gastroenterology 1987; 92: 118–124.
4. Hamilton S R Pathogenesis of columnar cell-lined (Barrett's) esophagus. In: Spechler S J, Goyal R K, eds. Barret's Esophagus: Pathophysiology, Diagnosis and Management. New York: Elsevier Science, 1985: P29–37.
5. Bremner C G, Lynch V P, Ellis F H Jr Barrett's esophagus: congenital or acquired?: an experimental study of esophageal mucosal regeneration in the dog. Surgery 1970; 68: 209–216.
6. Iascone C, DeMeester T, Little A, Skinner D. Barrett's esophagus, functional assessment, proposed pathogenesis and surgical therapy. Arch Surg 1983; 118: 543–549.
7. Flook D, Stoddard C. Gastroesophageal reflux (GOR) in patients with esophagitis or a columnar lined (Barrett's) esophagus. Gut 1983; 24: A1007.
8. Attwood S, DeMeester T, Bremner C, Barlow A, Hinder R. Alkaline gastroesophageal reflux: implications in the development of complications in Barrett's columnar lined lower esophagus. Surgery 1989; 106: 764–770.
9. Gillen P, Keeling P, Byrne P, Hennessy T. The pH profile of Barrett's esophagus. Br J Surg 1987; 74: 774–776.
10. Gillen P, Keeling P, Byrne P, Healy M, O'Moore R, Hennessy T. Implication of the duodenogastric reflux in the pathogenesis of Barrett's esophagus. Br J Surg 1988; 75: 540–543.
11. Kivilaakso E, Frommn D, Silen W. Effect of bile salts and related compounds on isolated esophageal mucosa. Surgery 1980; 87: 280–285.
12. Lambert R. Relative importance of biliary and pancreatic secretions in the genesis of esophagitis in rats. Am J Dig Dis 1962; 7: 1026–1033.
13. Lilliemoe K, Johnson L, Harmon J. Alkaline esophagitis: a comparison of the components of gastroduodenal contents to injure the rabbit esophagus. Gastroenterology 1983; 85: 621–628.
14. Haggit R, Tryzelaar J, Ellis F, Colcher H. Adenocarcinoma complicating columnar epithelium-lined Barrett's esophagus. Am J Clin Pathol 1978; 70: 1–5.
15. Reid B J, Weinstein W M, Lewin K J, Haggitt R C, VandeVenter G, DenBesten L, Rubin C E. Endoscopic biopsy can detect high grade dysplasia or early adenocarcinoma in Barrett's esophagus without grossly recognisable neoplastic lesions. Gastroenterol 1988; 94: 81.
16. DeMeester T, Attwood S, Smyrk T, Therkildsen D. Surgical therapy in Barrett's esophagus. Ann Surg 1990; 212: 528–542.
17. Streitz J Jr, Ellis F Jr, Gibb S, Balogh K, Watkins E Jr. Adenocarcinoma in Barrett's esophagus. A clinicopathological study of 65 cases. Ann Surg 1991; 213 (2): 122–125.
18. Barrett N. Chronic peptic ulcer of the esophagus and 'esophagitis'. Br J Surg 1950; 38: 175–182.
19. Naef A, Savary M, Ozello L. Columnar lined lower esophagus: an acquired lesion with malignant predisposition. Report on 140 cases of Barrett's esophagus with twelve adenocarcinomas. J Thorac Cardiovasc Surg 1975; 70: 826–834.
20. Skinner D, Walther B, Riddell R, Schmidt H, Iascone C, De Meester T. Barrett's esophagus: comparison of benign and malignant cases. Ann Surg 1983; 198: 554–566.
21. Hameeteman W, Tytgat G, Houthoff H J, VanDerTweel J. Barrett's esophagus: development of dysplasia and adenocarcinoma. Gastroenterology 1989; 96: 1249–1256.
22. Blot W J, Devesa S S, Kneller R W, Fraumeni J F. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991; 265: 1287–1289.
23. Powell J, McConkey C C. Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. Br J Cancer 1990; 62: 440–443.
24. Yang P C, Davis S. Incidence of cancer of the esophagus in the US by histological type. Cancer 1988; 61: 612–617.

25. Hesketh P J, Clapp R W, Doos W G, Spechler S J. The increasing frequency of adenocarcinoma of the oesophjagus. Cancer 1989; 64: 526–530.
26. Pera M, Cameron A, Trastek V, Carpenter H, Zinsmeister A. Increasing incidence of adenocarcinoma of the esophagus and the esophagogastric junction. Gastroenterology 1993; 104: 510–513.
27. Blot W, Devesa S, Fraumeni J Jr Continuing climb in the rates of esophageal adenocarcinoma: an update. JAMA 1993; 270: 1320.
28. Spechler S, Zeroogian J, Antoioli D, Wang H, Goyal R. Prevalence of metaplasia at the gastro-esophageal junction. Lancet 1994; 344: 1533–1536.
29. Sutton R, Herd J, Youngson J, Ashby D, Williams E M I. Increasing incidence of adenocarcinoma of the esophagus in both sexes within the Mersey region from 1963 to 1987. Proceedings of the 6th World Congress of the International Society for Diseases of the Esophagus. August, 1995; 120.
30. Attwood S, Smyrk T, De Meester T, Mirvish S, Stein H, Hinder R. Duodenoesophageal reflux and the development of esophageal adenocarcinoma in rats. Surgery 1992; 111: 503–510.
31. Pera M, Cardesa A, Bombi J, Ernst H, Pera C, Mohr U. Influence of esophago-jejunostomy on the induction of adenocarcinoma of the distalesophagus in Sprague-Dawley rats by subcutaneous injection of 2,6 dimethylnitrosomorpholine. Cancer Res 1989; 49: 6803–6808.
32. Mattsson H, Andersson K, Hakanson R, Larsson H, Sundler F, Wallmark B, Hassle A. Sex and species differences in plasma gastrin and gastrin dependant variables. Studies in rats and mice during omeprazole treatment. Gastroenterology 1988; 94: A291.
33. Brunner G, Creutzfeldt W, Harke U, Lamberts R. Therapy with omeprazole in patients with peptic ulcerations resistant to extended high dose ranitidine treatment. Digestion 1988; 39: 3–20.
34. Kaplan E L, Meier P. Nonparametric estimation from incoming observations. J Am Stat Assoc 1958; 53: 457–481.
35. Annesi I, Moreau T, Lellouch J Efficiency of logistic regression and cox proportional hazards models in longitudinal studies. Stat Med 1988; 8: 1515–1521.
36. Mirvish S, Rosinsky S. Biochemical and carcinogenesis studies on the rat esophagus: effects of N-nitroso compounds and possible tumor promoting agents. In: Pfeiffer C, ed. Cancer of the Esophagus, Vol. 2. Boca Raton, Florida: CRC Press, 1982: P215–217.
37. Seto Y, Kobori O, Shimizu T, Morioka Y. The role of alkaline reflux in esophageal carcinogenesis induced by N-amyl-N-Methylnitrosamine in rats. Int J Cancer 1991; 49: 758–763.
38. Pera M, Trastek V, Carpenter H, Fernandez P, Cardesa A, Mohr U, Pairolero P Influence of pancreatic and biliary reflux on the development of esophageal carcinoma. Ann Thorac Surg 1993; 55: 1386–1393.
39. Jankowski J, Hopwood D, Pringle R, Wormsley K. Increased expression of epidermal growth factor receptors in Barrett's esophagus associated with alkaline reflux: a putative model for carcinogenesis. Am J Gastroenterol 1993; 88: 402–408.
40. Yasui A, Hoeft S, Stein H, De Meester T, Bremner R. Gastric carcinoma. In: Nabeya K, Hanaoka T , Nogami H, ed. Diseases of the Esophagus. Tokyo: Springer Verlag, 1993: 169–172.
41. Kauer W, Burdiles P, Clark G, Peters J, Bremner C, De Meester T. Does duodenal juice reflux into the esophagus in complicated gastroesophageal reflux disease? Evaluation of a fiberoptic sensor for bilirubin. Proceedings of the 6th World Congress of the International Society for Diseases of the Esophagus. August 1995; 117.
42. Langhans P, Heger R, Hohenstein J, Bunte H. Operation-sequel-carcinoma – an experimental study. Hepato-Gastroenterol 1981; 28: 34–37.
43. Taylor P, Dowling R, Palmer T, Hanley D C, Murphy G M, Mason R C, McColl I. Induction of pancreatic tumors by longtern duodenogastric reflux. Gut 1989; 87: 1596–1600.
44. Mason R. Duodenogastric reflux in rat carcinoma. Br J Surg 1986; 73: 801–803.
45. Chomchai C, Bhadrachan N, Nigro N D. The effect of bile on the induction of experimental intestinal tumors in rats. Dis Col Rec 1974; 17: 310–313.
46. Houghton P, Mortensen N, Williamson R. Effect of duodenogastric reflux on gastric mucosal proliferation after gastric surgery. Br J Surg 1987; 74: 288–291.
47. Hikasa Y, Tanida N, Ohno T, Shimoyama T. Fecal bile acid profiles in patients with large bowel cancer in Japan. Gut 1984; 25: 833–838.
48. Jagelman D, DeCosse J, Bussey H, the Leeds Castle Polyposis Group. Upper gastrointestinal cancer in familial adenomatous polyposis. Lancet 1988; 1: 1149–1151.
49. Moorehead R, Campbell G, Donaldson J, McKelvey S. Relationship between duodenal bile salts and colorectal neoplasia. Gut 1987; 28: 1454–1459.
50. Sontang S, Schnell T, Chejfec G *et al*. Barrett's esophagus and colonic tumors. Lancet 1985; 1: 946–948.
51. Atwood S, Smyrk T, Marcus J *et al*. Effect of duodenal juice on DNA index and cell proliferation in a model of esophageal carcinoma. Br J Surg 1991; 78: A754.
52. Bartlen W, Liebermann-Meffert Feussner H, Stein H. Influence of pH on bile acid concentration in human, pig and commercial bile: implications for 'alkaline gastroesophageal reflux. Dis of Esophagus 1994; 7: 127–130.
53. Martin C, Shaw M, Ewing H, Machet D. Pancreatic reflux produces intestinal metaplasia in experimental columnar lined esophagus. Proceedings of the 6th World Congress of the International Society for Diseases of the Esophagus. August 1995; 225.
54. Quddus M R, Henley J D, Sulaiman R A, Palumbo T C, Gnepp D R. Helicobacter pylori infection and adenocarcinoma arising in Barrett's esophagus. Hum Pathol 1997; 28: 1007–1009.
55. Lord R V, Frommer D J, Inder S, Tran D, Ward R L. Prevelence of Helicobacter pylori infection in 160 patients with Barrett's esophagus or Barrett's adenocarcinoma. Aust N Z Surg 2000; 70 (1): 26–33.
56. Weston A P, Badr A S, Topalovski M, Cherian R, Dixon A, Hassanein R S. Prospective evaluation of the prevelence of gastric Helicobacter pylori infection in patients with GERD, Barrett's esophagus, Barrett's dysplasia, and Barrett's adenocarcinoma. Am J Gastroenterology 2000; 95: 387–394.
57. Correa P. A human model of gastric carcinogenesis. Cancer Res 1988; 48: 3554–3560.
58. Tersmette A, Offerhaus G, Tersmette K, Giardiello F M, Moore G W, Tytgat G N, Vandenbrouke J P. Meta analysis of the risk of gastric stump caner: detection of high risk patient subsets for stomach cancer after remote partial gastrectomy for benign conditions. Cancer Res 1990; 50: 6486–6489.
59. Caygill C, Hill M, Hall C, Kirkham Northfield T. Increased risk of cancer at multiple sites after gastric surgery for peptic ulcer. Gut 1987; 28: 924–928.
60. Caygill C, Hill M. Malignancy following surgery for benign peptic disease: a review. Ital J Gastroenterol 1992; 24: 218–224.
61. Mosbech J, Videbaek A. Mortality from and risk of gastric carcinoma among patients with pernicious anaemia. Br Med J 1950; 2: 390–394.
62. Ruddell W S, Bone E S, Hill M J, Walker C L. Pathogenesis of gastric cancer in anaemia. Lancet 1978; 1: 521–523.
63. Correa P, Cuello C, Duque E. Carcinoma and intestinal metaplasia of the stomach in Columbian migrants. J Nat Cancer Inst 1970; 44: 297–306.
64. Chen V, Abu-Elyazeed R, Zavala D. Risk factors of gastric precancerous lesions in a high risk Columbian population. II. Nitrate and Nitrite. Nutr Cancer 1990; 13: 67–72.
65. Walters C L, Downes M J, Edwards M W, Smith P L R. Determination of a non-volatile N-nitrosamine on a food matrix. Analyst 1978; 103: 1127–1133.
66. Bavin P M G, Darkin D W, Viney N J. Total nitroso compounds in gastric juice. In: N-nitroso compounds: occurrence and biological effects. IARC Publication no. 41. Lyon: IARC 1982: 337–344.
67. Sobala G, Pignatelli B, Schorah C *et al*. Levels of nitrite, nitrate, N-nitroso compounds, ascorbic acid and total bile acids in gastric juice of patients with and without precancerous conditions of the stomach. Carcinogenesis 1991; 12: 193–198.
68. Dayal Y, DeLellis R, Wolfe H. Hyperplastic lesions of the gastrointestinal endocrine cells. Am J Surg Pathol 1987; 2 (Suppl.): 87–101.

69. Larsson H, Carlsson E, Mattson H *et al*. Plasma gastrin and gastric enterochromaffin-like cell activation and proliferation: studies with omeprazole and ranitidine in intact and antrectomised rats. Gastroenterology 1986; 90: 391–399.
70. Johnson L. New aspects of the trophic action of gastrointestinal hormones. Gastroenterology 1977; 67: 453–459.
71. Sirinek K, Levine B, Moyer M. Pentagastrin stimulates in vitro growth of normal and malignant human colon epithelial cells. Am J Surg 1985; 149: 35–39.
72. McGregor D, Jones R, Karlin D, Romsdahl M M. Trophic effects of gastrin on colorectal neoplasms in the rat. Ann Surg 1982; 195: 219–223.
73. Sumiyoshi H, Yasui W, Ochiai A, Tahara E. Effect of gastrin on tumor growth and cyclic nucleotide metabolism in xenotransplantable human gastric and colonic carcinomas in nude mice. Cancer Res 1984; 44: 4276–4280.
74. Watson S, Durrant L, Morris D. Growth-promoting action of gastrin on human colonic and gastric tumor cells cultured in vitro. Br J Surg 1988; 75: 342–345.
75. Simopoulos C, Gaffen J, Bennett A. Effects of gastrointestinal hormones on the growth of human intestinal epithelial cells. Gut 1989; 30: 600–604.
76. Smith J, Solomon T. Effects of gastrin, proglumide, and somatostatin on growth of human colorectal cancer. Gastroenterology 1988; 95: 1541–1548.
77. Charnley R, Thomas W, Stanley J, Morris D. Serum gastrin concentrations are higher in colorectal patients. Gut 1989; 30: A712.
78. Karakai Y, Shimazaki K, Nakamura K *et al*. Effect of hypergastrinaemia in chemical carcinogenesis of the esophagus in rats. In: Skinner D, Little A, Ferguson M. eds. Diseases of the Esophagus. Chicago: Springer-Verlag, 1990: Chapter 25.
79. Lind T, Cederberg C, Forssell H, Olausson M, Olbe L. Relationship between reduction of gastric acid secretion and plasma gastrin concentration during omeprazole treatment. Scand J Gastroenterol 1988; 23: 1259–1266.
80. Langman M. Postmarketing surveillance and the examination of the long term safety of anti ulcer drugs. Balliere's Clin Gastro 1993; 7: 183–190.
81. Moller D, Lindvig K, Lefter R, Mosbech J, Moller J. Cancer occurrence in a cohort of patients treated with cimetidine. Gut 1989; 30: 1158–1562.
82. Vecchia C, Negri E, D'Avanzo B, Franceschi S. Histamine-2-receptor antagonists and gastric cancer risk. Lancet 1990; 36: 355–357.
83. Wallmark B, Jaresten B, Larsson H, Rydberg B, Brandstrom A, Fellenius E. Differentiation among inhibitory actions of omeprazole, cimetidine and SCN^- on gastric acid secretion. Am J Physiol 1983; 245: G64–G71.
84. Helander H, Ramset C, Regardh C. Localisation of omeprazole and metabolites in the mouse. Scan J Gastro Enterol 1986; 20 (Suppl. 108): 95–104.
85. Jines D, Howden C, Burget D, Kerr G, Hunt R. Acid suppression in duodenal ulcer: a metaanalysis to define optimal dosing with antisecretory drugs. Gut 1987; 28: 1120–1127.
86. Sharma B, Santana I, Wood E *et al*. Intragastric bacterial activity and nitrosation before, during and after treatment with omeprazole. Br Med J 1984; 298: 717–719.
87. Festen H, Thijs J, Lamera C. Effect of oral omeprazole on serum gastrin and pepcinogen I levels. Gastroenterology 1984; 87: 1030–1034.
88. Creutzfeldt W, Stockmann F, Conlon J, Folsch U, Bonatz G, Wulfrath M. Effect of short-term and long-term feeding of omeprazole on rat gastric endocrine cells. Digestion 1986; 35 (Suppl. 1): 84–97.
89. Hakanson R, Bottcher G, Sundler F, Vallgren S. Activation and hyperplasia of gastrin and enterochromaffin-like cells in the stomach. Digestion 1986; 35 (Suppl. 1): 21–41.
90. Ekman L, Hansson E, Havu N, Carlsson E, Lundberg C. Toxicological studies on omeprazole. Scand J Gastroenterology 1985; 20 (Suppl. 108): 53–69.
91. Havu N. Enterochromaffin-like cell carcinoids of gastric mucosa in rats after life-long inhibition of gastric secretion. Digestion 1986; 35 (Suppl. 1): 42–55.
92. Lundell L, Backman L, Ekstrom L *et al*. Prevention of relapse of reflux esophagitis after endoscopic healing: efficacy and safety of omeprazole compared with ranitidine. Scand J Gastroenterol 1991; 26 (3): 248–256.
93. Carlsson E. A review of the long term effects of acid inhibition in animals. Scand J Gastroenterol 1989; 24 (Suppl. 166): 19–23.
94. Brunner G, Creutzfeldt W. Omeprazole in the long term management of patients with acid related diseases resistant to ranitidine. Scand J Gastroenterology 1989; 24 (Suppl. 166): 101–105.
95. Koop H, Wachmann H, Eissede R, Arnold R. Efficacy and safety of long term omeprazole maintenance therapy in H2 blocker-resistant reflux esophagitis. Gastroenterology 1990; 98: A70.
96. Maton P, Vinayek R, Frucht H *et al*. Long term efficacy and safety of omeprazole in patients with Zollinger–Ellison syndrome: a prospective study. Gastroenterology 1989; 97: 827–836.
97. Solvell A. Clinical safety of omeprazole. Digestion 1990; 47 (Supp): 59–63.
98. Dent J. Australian clinical trials of Omeprazole in the management of reflux esophagitis. Digestion 1990; 47 (Suppl. 1): 69–71.
99. Holt S, Howden C. Omeprazole: overview and opinion. Digestive Dis And Sci 1991; 36: 385–393.

Aust. N.Z. J. Surg. (1998) **68**, 209–212

ORIGINAL ARTICLE

STAGING OF OESOPHAGEAL CARCINOMA BY ENDOSCOPIC ULTRASOUND: PRELIMINARY EXPERIENCE

T. PHAM, E. ROACH, G. L. FALK, J. CHU, M. C. NGU AND D. B. JONES

Gastrointestinal Ultrasound Research Unit, Concord Repatriation General Hospital, Sydney, Australia.

Background: Endoscopic ultrasound (EUS) is a relatively recent imaging modality that is capable of visualizing oesophageal tissue layers and para-oesophageal structures. Current pre-operative staging of oesophageal cancer is less than satisfactory, and a modality which may improve pre-operative staging, thus allowing a more rational approach to choice of treatment, may be a welcome addition to current techniques. The purpose of the present study was to evaluate the accuracy of EUS in the staging of oesophageal carcinoma in a consecutive cohort of patients.

Methods: Forty-three patients with oesophageal cancer were prospectively staged with EUS using the radial scanning Olympus EUM-3 echo-endoscope. In the 28 patients who underwent surgery EUS staging was correlated with operative and histological findings to evaluate the EUS accuracy rate of assessing tumour depth (T stage), and the presence of nodal involvement (N stage) using internationally accepted TNM staging criteria.

Results: Endoscopic ultrasound accuracy rates for overall T-staging was 61% whereas that of N-staging was 75%. The overall TNM pathological staging was 75% accurate by EUS.

Conclusions: Compared to published literature figures for oesophageal staging by computed tomography scanning (39–54%) these results demonstrate that EUS has a reasonable accuracy rate for staging. Endoscopic ultrasound may prove to be a useful additional modality in the management of oesophageal cancer.

Key words: endoscopic ultrasound, oesophageal cancer, staging.

INTRODUCTION

Oesophageal carcinoma often presents at an advanced stage and, despite advances in diagnosis, staging and treatment, the majority of patients will die from their disease.[1] Although there is a broad range of therapies available for oesophageal cancer, ideally the choice of treatment should be based on the projected outcome of any such treatment for that individual. Disease stage has been shown to correlate with probability of survival following surgical[2,3] and non-surgical[4] treatments. Depth of invasion (T stage), regional lymph node status (N stage) and the presence or absence of distant metastases (M stage) are therefore important determinants of prognosis.

Accurate pre-operative staging is therefore desirable in deciding between curative or palliative surgery or relief of dysphagia by non-operative means. To date, computed tomography (CT) has been the main imaging modality used in the pre-operative staging of oesophageal carcinoma. The development of endoscopic ultrasound (EUS) with its ability to visualize oesophageal tissue layers and para-oesophageal structures potentially allows more accurate staging of oesophageal carcinoma than CT scanning.[5,6] The report presented here examines our early experience in the application of EUS for the pre-operative staging of oesophageal carcinoma, compared with the 'gold standard' of operative and histological confirmation.

Correspondence: Dr D. Brian Jones, Gastroenterology Unit, Concord Repatriation General Hospital, NSW 2139, Australia.
Email: dbjones@ozE-mail.com.au

Accepted for publication 3 September 1997.

METHODS

Endoscopic ultrasound was performed with the Olympus EUM-3 instrument (Tokyo, Japan) under intravenous sedation with midazolam plus or minus pethidine. The echo-endoscope with the ultrasound transducer located at the instrument tip surrounded by a water-filled balloon (Fig. 1) allows a 360° image of the oesophageal wall with its five layers[7] (Fig. 2). The five-layered structure of the oesophagus as visualized by EUS consists of mucosal interface, muscularis mucosae, submucosa, muscularis propria and adventitia (Fig. 2).

Forty-three consecutive patients with squamous and adenocarcinoma of the oesophagus underwent EUS in addition to other imaging including barium studies, endoscopic assessment of tumour length, and CT scans of the thorax and abdomen. Based on fitness for surgery (mainly age and coexisting cardiorespiratory disease), CT evidence of extensive distant metastases, and EUS evidence of extensive mediastinal involvement and invasion of adjacent structures, 15 cases did not undergo surgical exploration. The decision not to operate was made by a multidisciplinary team including physicians, surgeons and medical oncologists and radiotherapists. A cohort of 28 cases therefore had both a pre-operative EUS study and subsequent surgical/pathological staging. Most surgical cases were operated on by one surgeon (G. L. F.). Pre-operative EUS was recorded on videotapes and reported by one ultrasonologist (J. C.), who also assisted at the EUS examination, without knowledge of subsequent pathology findings.

Of the 28 cases there were 20 men and eight women with an age range of 51–80 years (mean, 67.5). Subsequent histology confirmed 18 squamous cell carcinoma and 10 adenocarcinoma. All EUS studies of oesophageal carcinoma cases were reported according to the TNM staging method (T: tumour, N: node, M:

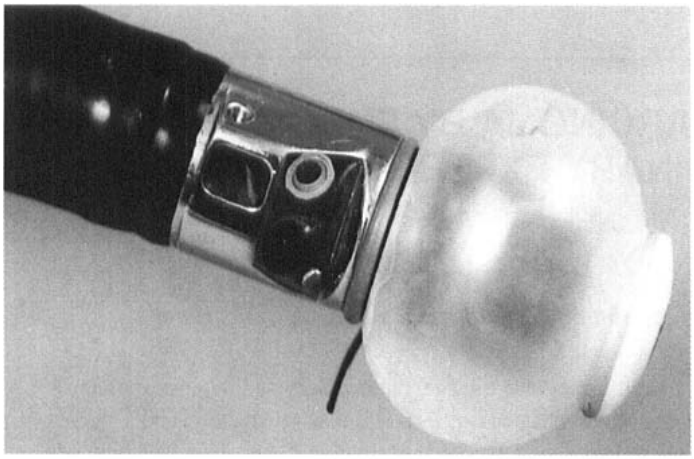


Fig. 1. Photograph of the tip of the EUS endoscope showing the ultrasound transducer surrounded by a water-filled balloon.

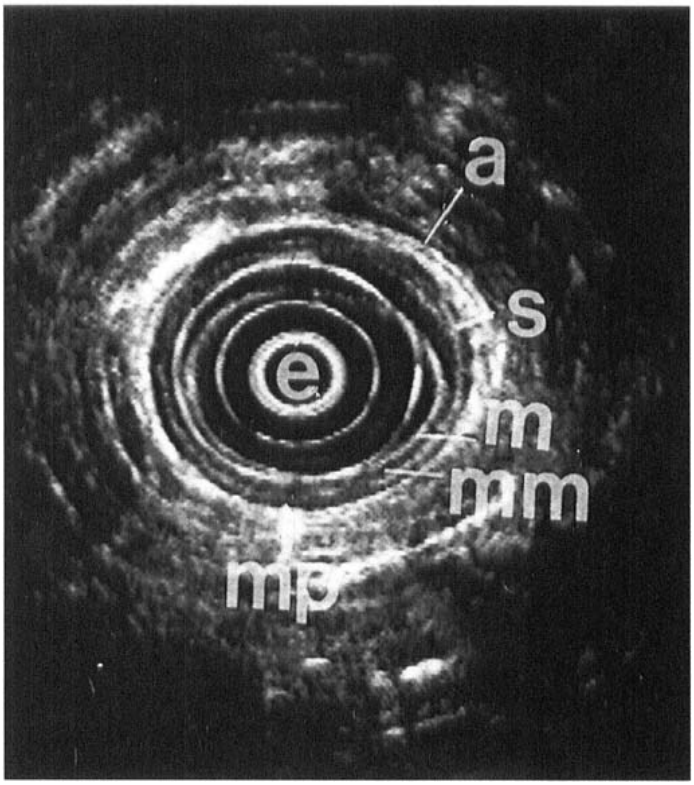


Fig. 2. Endoscopic ultrasound image of a normal oesophageal wall with its five layers (e, endoscope; m, mucosal interface; mm, muscularis mucosae; s, submucosa; mp, muscularis propria; a, adventitia).

Table 1. TNM staging classification

Tumours	
T1	Tumour localized in mucosa or sub-mucosa.
T2	Tumour with infiltration into muscularis propria.
T3	Tumour with penetration into adventitia.
T4	Tumour with infiltration into adjacent structures.
Lymph nodes	
N0	No nodal involvement.
N1	Regional lymph node metastases.
Metastases	
M1	Celiac lymph node or liver metastases.
Stage	
I	T1 N0 M0
II	T2/T3 N0 M0 or T1/T2 N1 M0
III	T3 N1 M0 or T4, any N, M0
IV	Any T, any N, M1

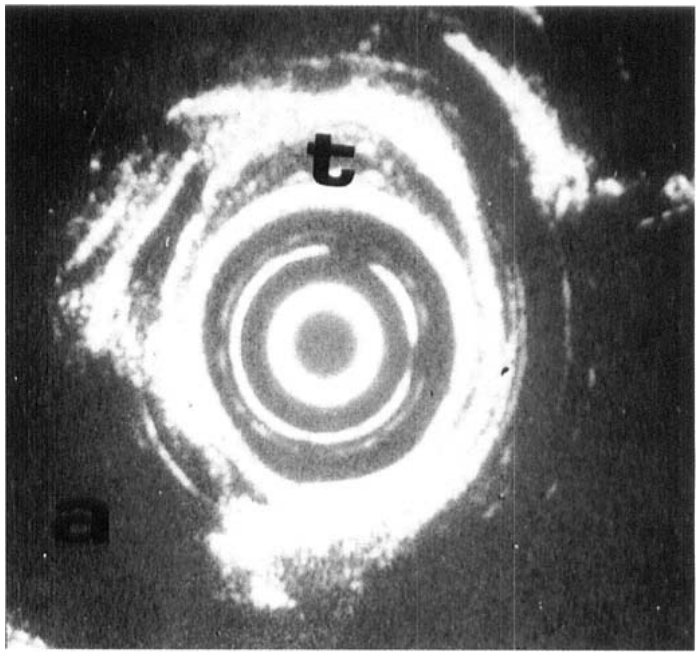


Fig. 3. An example of a T1 lesion with tumour localized in mucosa and submucosa (t, tumour; a, thoracic aorta).

metastases)[8] as shown in Table 1. At surgery, the surgeon assessed invasion of adjacent structures. Resected specimens were submitted for routine histological examination. The examining histopathologist reported depth of invasion and microscopic involvement of lymph nodes according to established TNM classification for oesophageal cancer.

RESULTS

There were only two cases where the echo-endoscope was unable to be passed through the tumour due to tight stenosis. Due to the risk of perforation it was decided not to perform oesophageal dilatation before EUS in patients with stenosis. Figure 3 shows an example of a T1 lesion with the tumour localized to mucosa and submucosa. Figure 4 shows an extensive T4 tumour with disruption of all layers and spread beyond the oesophageal adventitia and Fig. 5 demonstrates a T3 lesion with a contiguous lymph node present.

Results of pre-operative EUS staging compared with post-operative histological staging with respect to T- and N-stages are shown in Table 2. It can be seen that stage T3, having almost half of all the cases, also has the highest accuracy rate of 85%, whereas that of other stages is only 40%. The overall accuracy rate of EUS in T-staging is 61%. For N-staging the overall accuracy rate is 75% with 88% of N1 being accurately staged by EUS. In the T-staging there are more cases overstaged than understaged (7 *vs* 4). Similarly there was more error in overstaging lymph nodes than understaging (5 *vs* 2).

Results of overall TNM staging are displayed in Table 3, where 43% of cases were in stage III and the accuracy of EUS for this stage is 92%. The overall accuracy rate for all stages is 75%.

DISCUSSION

It has been shown that three independent variables are closely correlated with the post-resection prognosis of oesophageal carcinoma; namely, depth of mucosal infiltration, lymph node metastases and distant secondaries.[8] The reported accuracy rate for

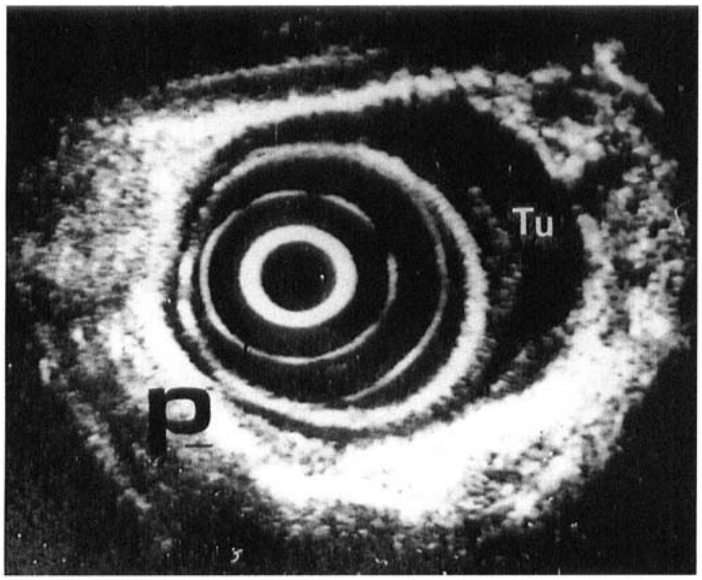


Fig. 4. An example of a T4 lesion with tumour spreading beyond the adventitia (Tu, tumour; p, pleural reflection).

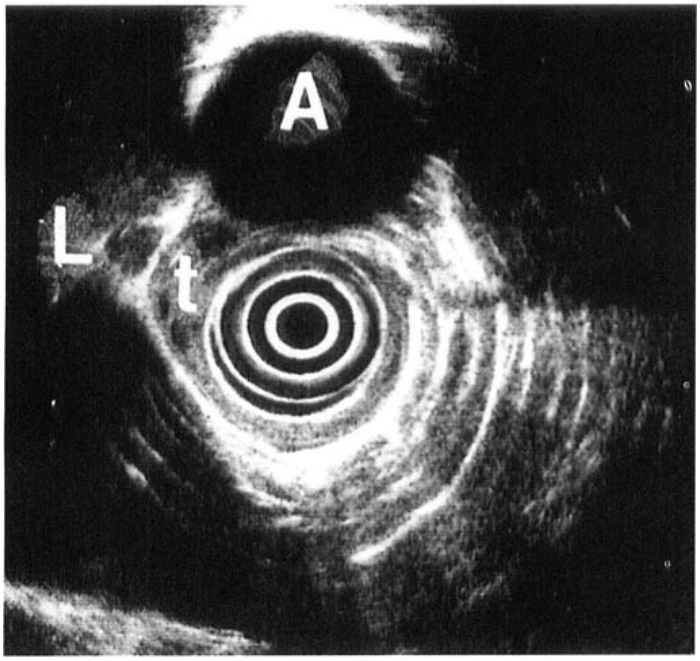


Fig. 5. An example of malignant lymph node adjacent to a T3 tumour (L, lymph node; t, tumour; A, aorta).

Table 2. Accuracy rates of EUS in local (T/N) staging

	n	Correct	Over-staged	Under-staged	Accuracy (%)
T1	5	2	3	0	40
T2	5	2	3	0	40
T3	13	11	1	1	85
T4	5	2	0	3	40
Overall	28	17	7	4	61
			False positive	False negative	
N0	12	7	5	0	58
N1	16	14	0	2	88
Overall	28	21	5	2	75

Table 3. Accuracy rates of EUS in overall staging of oesophageal carcinoma

Stage	*n*	Correct	Over-staged	Under-staged	Accuracy (%)
I	3	2	1	0	67
II	9	6	3	0	67
III	12	11	0	1	92
IV	4	2	0	2	50
Overall	28	21	4	3	75

T-stage in different series with EUS is 72–92% and for N-stage 50–90%.[8] In the current study the overall accuracy figure is 75%, stage III being the most common (12/28 cases) and the most accurately staged (92%). The current study does show lower accuracy rates for both T- and N-staging compared to the literature. This almost certainly represents the 'learning curve' for EUS. A recent study has shown that the overall accuracy in their experience was 58% in the first 100 endosonographies, but this rose to 83% in the next 100 cases.[9] In early lesions, overinflation of the EUS balloon may give a spuriously high impression of depth of invasion due to physical compression of tumour into normal oesophageal tissue thus causing 'pseudo-invasion'. In stenosing lesions the full depth of tumour invasion may not be appreciated and EUS may give an underestimate of depth of invasion. Other studies have confirmed the impression that non-traversable strictures represent advanced (usually T4) disease[10,11] and EUS may add little to the staging process apart from a tendency to understage. One study suggested an additional benefit from pre-EUS dilatation in such cases,[10] but a complementary study[11] advised against dilatation on the basis of a 24% perforation rate with little addition to staging information if one accepts that stricture *per se* represents advanced disease.

Assessing nodal involvement is complicated by the fact that normal-sized lymph nodes can harbour metastases while enlarged nodes may only be due to reactive hyperplasia.[7] A pathognomonic pattern of lymph node metastases is a direct extension of the transmural carcinomatous infiltration into the adjacent lymph node[7] (as in Fig. 5). Using a size criterion of 10 mm, the accuracy rate in our series for lymph node staging is 75% with a positive predictive value of 81% and a negative predictive value of 78%, similar values having been noted elsewhere.[12]

There was not the opportunity in the present study to compare the results of EUS with those of CT scanning because not all patients had undergone CT scans, and a number of patients were referred from outside this institution and access to previous radiology was not always possible. In general, the literature[13] suggests a lower accuracy rate of CT compared with that of EUS for TNM staging (e.g. 89 *vs* 59% for T-stage and 80 *vs* 50% for N-stage). Although CT scanning is less accurate in assessment of depth of tumour invasion, it is invaluable in assessment of distant metastases. It may also yield additional information in the situation where there is a non-traversable oesophageal stricture. It has been suggested that combining EUS for local and CT for distant staging will increase the accuracy rate from 64% with CT alone to 86% for the combined modalities.[5]

The present study demonstrates that in our experience EUS has an accuracy of 61% for T-staging, 75% for N-staging, and an overall accuracy of 75%. Taken in isolation, such accuracy figures are

not sufficient figures on which to base clinical decision analysis for management of patients with oesophageal cancer. Endoscopic ultrasound, however, may be regarded as complementary to other modalities such as CT, and the study supports the findings of others[5,6,9,11–15] which suggest that EUS may prove to be a useful adjunct in the pre-operative selection and overall management strategy of patients with oesophageal carcinoma.

REFERENCES

1. Coia LR, Sauter ER. Esophageal cancer. *Curr. Probl Cancer* 1994; **18**: 189–247.
2. Skinner D, Ferguson M, Sonano A *et al.* Selection of operation for esophageal cancer based on staging. *Ann. Surg.* 1986; **27**: 391–401.
3. Ellis FH Jr, Watkins E, Krasna MJ *et al.* Staging of carcinoma of the esophagus and cardia: A comparison of different staging criteria. *J. Surg. Oncol.* 1993; **55**: 231–5.
4. Stampfli C, Souquet JC, Napoleon PJ *et al.* Squamous cell carcinoma of the esophagus: Medical or surgical treatment? (Abstract). *Gastrointest. Endosc.* 1992; **28**: 242.
5. Botet JF, Lightdale CJ, Zauber AG *et al.* Preoperative staging of oesophageal cancer: Comparison of endoscopic ultrasound and dynamic CT. *Radiology* 1991; **181**: 419–25.
6. Vilgrain V, Mompoint D, Palazzo L *et al.* Staging of oesophageal cancer: Comparison of results with endoscopic sonography and CT. *Am. J. Roentgen.* 1990; **155**: 277–81.
7. Tytgat G, Tio TL. Oesophageal ultrasonography. *Gastroenterol. Clin. North Am.* 1991; **20**: 659–67.
8. Beahrs OH, Henson D, Hutter RVP, Myers MH (eds). *Manual for Staging Cancer,* 3rd edn. Philadelphia: Lippincott, 1988; 63–7.
9. Fockens P, Van den Brande JHM, van Dullemen HM *et al.* Endosonographic T-staging of esophageal carcinoma: A learning curve. *Gastrointest. Endosc.* 1996; **44**: 58–62.
10. Kallimanis GE, Gupta PK, Al-Kawas FH *et al.* Endoscopic ultrasound (EUS) for staging oesophageal cancer, with or without dilation, is clinically important and safe. *Gastrointest. Endosc.* 1995; **41**: 540–6.
11. Catalano MF, Van Dam J, Sivak MV. Malignant esophageal strictures: Staging accuracy of endoscopic ultrasonography. *Gastrointest. Endosc.* 1995; **41**: 535–9.
12. Rosch T, Lorenz R, Zenker K *et al.* Local staging and assessment of resectability in carcinoma of the oesophagus, stomach and duodenum by endoscopic ultrasonography. *Gastrointest. Endosc.* 1992; **38**: 460–7.
13. Tio TL, Cohen P, Coene PP *et al.* Endosonography and CT of oesophageal carcinoma. *Gastroenterology* 1989; **96**: 478–86.
14. Quint LE, Glazer GM, Orringer MB, Gross BH. Oesophageal carcinoma: CT findings. *Radiology* 1985; **155**: 171–5.
15. Fekete F, Gayet B, Frija J. CT scanning in the diagnosis of oesophageal disease. In Jamieson G (ed.). *Surgery of the Oesophagus,* 1st edn. Edinburgh: Churchill Livingstone, 1988; 87–91.

Diseases of the Esophagus (1997) **10**, 145–148

CASE REPORT

Carcinoma of the esophagus treated with radical chemoradiation 19 years after irradiation for recurrent breast cancer

C. MacLeod*, E. Moylan†, G. L. Falk**

**Department of Radiation Oncology, Royal Prince Alfred Hospital, Camperdown, 2050, †Department of Medical Oncology, Concord Repatriation Hospital, Concord, 2138 and **Medical Director, Sydney Oesophageal Services, PO Box 1085, Strathfield, 2135 New South Wales, Australia*

SUMMARY. Prior irradiation to a site is a relative and often absolute contraindication to further irradiation because the tolerance dose of normal tissues is usually exceeded and therefore the risk of serious long-term side-effects is high. This case report describes radical salvage chemoradiation for an esophageal carcinoma in a patient who had prior high-dose neck and chest wall irradiation for the management of a breast cancer 19 years previously.

THE CASE

A 59-year-old woman presented with a 3-month history of increasing dysphagia and weight loss of 8 kg (13% of total weight). On investigation a 3 cm moderately differentiated squamous cell carcinoma was found at the junction of the cervico-thoracic esophagus, 18–21 cm from the incisors. There was no evidence of systemic metastasis. The CT scan showed no evidence that the carcinoma had invaded mediastinal structures and at the bronchoscopy there was no involvement, nodularity or inflammation of the trachea observed; however, at surgery the cancer was found to be firmly adherent to the trachea and the procedure was abandoned. She was referred for radical chemoradiation as a salvage treatment.

She had a significant past history of a T2 N1 adenocarcinoma of the left breast treated in February 1975 with a mastectomy and axillary dissection; three of the nine resected nodes contained metastatic cancer. Six months after her original surgery she had a 4 cm axillary relapse and was treated with surgical resection and with post-operative radiotherapy to the chest wall, axilla and supraclavicular nodal areas to a peak dose of 50 Gray (Gy) in 20 fractions using a cobalt teletherapy unit. Symptomatic esophagitis resulted from this treatment. The rest of the history was unremarkable; in particular, she had never smoked, alcohol consumption was rare and she had not had esophageal motility problems or anemia.

On examination she looked well with no evidence of supraclavicular lymphadenopathy or systemic metastasis. She had an asymptomatic moderate size goitre. On close inspection of her left mastectomy site, there was induration and telangiectasia over the lower part of the sternum and in the axilla, and the CT scan demonstrated some left upper lobe fibrosis also consistent with late side-effects from irradiation (Fig. 1).

MANAGEMENT

The patient received combined modality treatment with chemotherapy and radiation and had two cycles of cisplatin (75 mg/m^2 on the first day of each course) and 5 fluorouracil (800 mg/m^2 continuous infusion days 1–4) prior to the irradiation, and two cycles concurrently with the irradiation on the first and fifth week of the radiotherapy, at 4 week intervals and was given a radiation dose of 45 Gy in 25 fractions in 5 weeks with no treatment breaks. The chemotherapy was well tolerated and produced moderate nausea and neutropenia but there were no infections. The chemoradiation produced a severe acute reaction with moist desquamation over the anterior and lateral neck and a confluent mucositis. These acute reactions had largely settled 6 weeks after treatment.

The radiation delivery was optimized by using CT planning to delineate the target volume, customized immobilization and shielding to protect normal structures

Correspondence to: **Craig MacLeod,** Department of Radiation Oncology, Royal Prince Alfred Hospital, Missenden Road, Camperdown, NSW 2050, Australia.

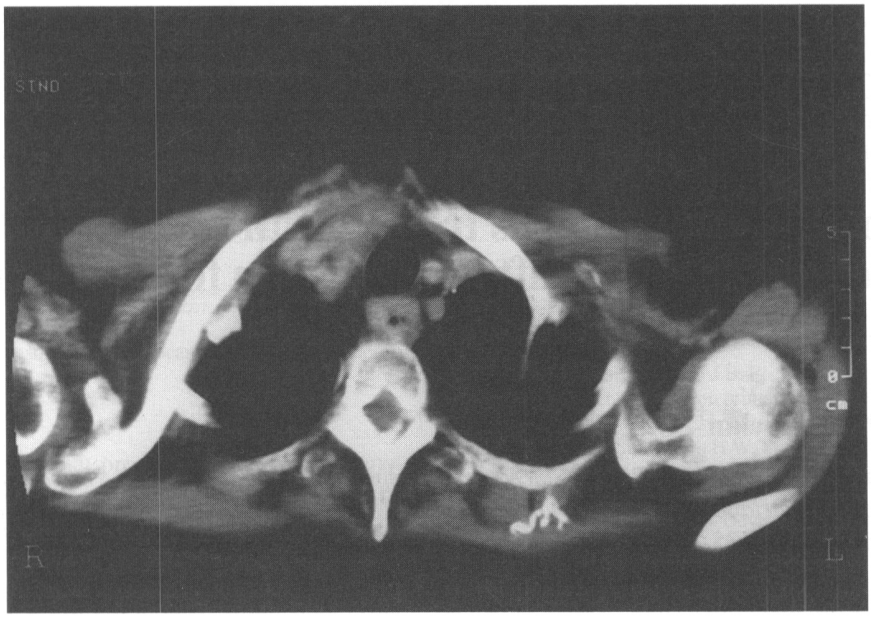


Fig. 1 Pre-treatment CT scan of thoracic inlet demonstrates esophageal thickening, a multinodular goitre and a line of fibrosis in the left lung from the previous irradiation.

where possible, and calculations were performed on multiple planes and compensators were used to minimize dose variation through the treatment volume. The dose of irradiation was slightly reduced from the dose (50 Gy) used with concurrent chemotherapy in the pivotal intergroup study[1] because of concerns about potential late toxicity.

OUTCOME

There was a complete response to the treatment and the patient remains alive and well without evidence of recurrent disease at 25 months. She had continuing but less severe dysphagia and follow-up endoscopy showed a benign stricture that was dilated with an excellent symptomatic response. There have been no serious long-term side-effects from the treatment at this stage. The most feared complication was myelopathy which has a median onset of 12 months.[2] Interestingly, the goitre regressed but there was no biochemical evidence of hypothyroidism. There were cosmetic skin changes with patchy hyperpigmentation and hypopigmentation over the neck, more prominent on the left, and a horizontal line of fibrosis across the upper anterior left chest wall (Fig. 2).

DISCUSSION

This 59-year-old woman posed the difficult management problem of an inoperable squamous cell carcinoma of the esophagus in a site that had received prior irradiation. The principal questions raised were: did the previous radiation cause the cancer?; what dose of radiation had she previously received to dose limiting critical tissues and, in particular, the spinal cord?; and finally, based on this previous dose, what further dose, if any, could be safely given?

Radiation is well documented to be mutagenic and carcinogenic. Whereas, radiation-induced leukemias follow an absolute risk model and there is a discrete crop of leukemias above the spontaneous level, solid cancers follow a relative risk model and the natural incidence is increased by a constant factor. The latency periods are also very different with a short latency for radiation induced leukemias of as little as 5 years but a latency often around 20 years for solid cancers.[2]

Specifically addressing the question of whether irradiation for breast cancer causes cancer of the esophagus, a cancer-based registry study of 41 109 women with breast cancer diagnosed between 1935 and 1982 demonstrated a slightly higher risk of developing a subsequent cancer of the esophagus if prior radiation had been given, although the nature of the association was unclear as the radiation fields received were not noted.[3] It certainly appears that the incidence of other solid cancers is increased and a case-control study found an excess of lung cancers within the previously irradiated volume in women who had received breast or chest wall irradiation for breast cancer and there was a multiplicative effect observed in women who smoked.[4] The esophagus would not have received the peak dose but a dose of approximately 35 Gy similar to the dose used in mantle irradiation for Hodgkin's disease. Of three large studies of second cancers in Hodgkin's disease,[5–7] where the whole esophagus was commonly irradiated, one study found an excess risk of subsequent esophageal malignancy.[7] However, the nature of the association was unclear as the type of treatment received, whether radiotherapy or chemotherapy, was

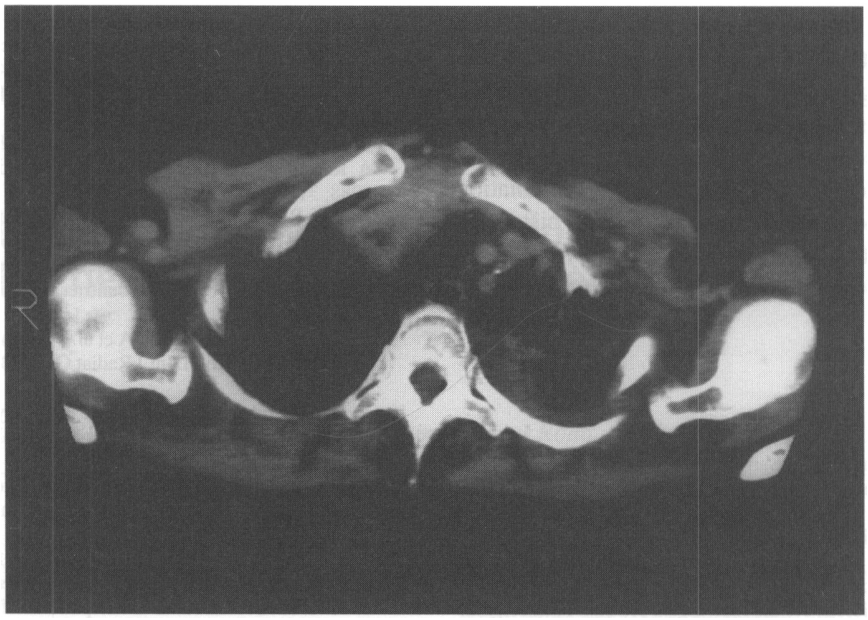


Fig. 2 Post-treatment CT scan of thoracic inlet demonstrates resolution of the esophageal thickening and more severe left-lung fibrosis. The irradiated volume was symmetrical and the left pulmonary fibrosis is consistent with this site receiving prior irradiation.

not documented. Therefore, although there is not clear evidence implicating radiation to have a causal role in esophageal cancer, the timing of this woman's malignancy, the anecdotal clinical evidence, and lack of other risk factors are strongly suggestive of an association.

The second question was what dose of radiation had particular sites received? The original radiotherapy prescription did not detail field centres but the standard technique at the time at this hospital was to treat the supraclavicular field to midline with no angulation away from the cord, and there was a 1 cm gap on the skin between the supraclavicular field and the tangential chest wall fields. To calculate the previous dose received by structures, the assumption was made that the patient's neck shape had not altered and that the whole width of the spinal cord was irradiated by exit dose from the supraclavicular field, because of divergence of the radiation beam at depth. Based on these assumptions the dose to the spinal cord was calculated to be 28 Gray in 20 fractions. Obviously, significant amounts of normal tissue situated anterior to the spinal cord received higher doses and some including subcutaneous tissues, lung and half the larynx had received tumor dose.

The final question was what further dose of radiation could be given? In general, irradiation is given to a specific tolerance dose rather than to a specific tumoricidal dose. Current practice of radiation therapy is influenced by documented tolerance doses and these are referred to as the TD 5/5 (the probability of a 5% severe complication rate within 5 years) and the TD 50/5 (the probability of a 50% severe complication rate within 5 years). Published tables of tolerance doses exist for most normal tissues and are, in general, based on outcome data from general radiation trials and retrospective reports rather than specific dose escalation or dose response trials.[8] The data exist for whole and partial organ irradiation and the data are for adult normal tissues given in conventional fractionation, that is, 1.8–2.0 Gy fractions.

However, in the previously irradiated volume, a hypofractionated course had been given and the increased dose per fraction produces proportionately more late, normal tissue toxicity compared with standard fractionation. This effect is expressed mathematically as the linear quadratic equation, which can be used to convert high dose per fraction to the biologically equivalent dose (BED) in standard 2 Gy fractions. This converts 50 Gy in 2.5 Gy fractions to a BED of 60 Gy for late toxicity.[9] Therefore, the radiation given for the esophageal cancer grossly exceeded these limits; for example, the TD 50/5 of skin, lung and larynx were exceeded, with BED doses of around 100 Gy for clinically significant volumes. The TD 5/5 of the spinal cord was exceeded but modestly with a peak calculated dose of 52 Gy.

A radiation oncology dogma is that radiation dose tolerance is cumulative and any given site or organ can only safely receive its tolerance dose even if partial tolerance doses are given months or, in this case, years apart. There is both experimental and anecdotal clinical evidence that there is repair of radiation damage if treatment is separated by significant periods of time and the tolerance dose is therefore increased.[10–12] However, as a prudent practice, it is the exceptional clinical circumstance where retreatment to above tolerance is instituted. Such was the clinical situation here, where radical surgery was not technically possible. Of note, tolerance doses are conservative values and retrospective reviews have reported no serious complications when treating large numbers of patients with higher doses.[13–14]

In summary, this case report supports a relationship between irradiation and the late development of esophageal malignancy. The good response to chemo-radiation and absence of serious side-effects possibly reflect both the conservative estimates of normal tissue tolerance to irradiation and some repair of radiation damage over a period of years. Therefore, a history of previous irradiation should not absolutely preclude attempted curative treatment in a similar situation.

REFERENCES

1. Herskovic A, Martz K, Al-Sarraf M et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med 1992; 24: 1593–1598.
2. Schultheiss T E, Stephens C L. Permanent radiation myelopathy. Br J Rad 1992; 65: 735–737.
3. Hall E J. Radiobiology for the radiologist. 3rd edn. Philadelphia: Lippincott, 1988, chapter 19: 385–411.
4. Harvey E B, Brinton L A. Second cancer following cancer of the breast in Connecticut. Nat Cancer Inst Monogr 1985; 68: 99–112.
5. Neuget A I, Murray T, Santos J, Amols H, Hayes M K, Flannery J T, Robinson E. Increased risk of lung cancer after breast cancer radiation therapy in cigarette smokers. Cancer 1994; 73: 1541–1543.
6. Swerdlow A J, Douglas A J, Hudson B V, Hudson G V, Bennett M H, MacLennan K A. Risk of second cancers after Hodgkin's disease by type of treatment: analysis of 2846 patients in the British National Lymphoma Investigation. Br Med J 1992; 304; 1137–1143.
7. Tucker M A, Coleman C N, Cox R S, Varghese A, Rosenberg S A. Risk of second cancers after Hodgkin's disease. N Engl J Med 1988; 318: 76–81.
8. Sankila R, Garwicz S, Olsen H et al. Risk of subsequent malignant neoplasms among 1641 Hodgkin's disease patients diagnosed in childhood and adolescence: a population-based cohort study in five Nordic countries. J Clin Oncol 1996; 14: 1442–1446.
9. Emami B, Lyman J, Brown A et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys 1991; 21: 109–122.
10. Barton M. Tables of equivalent dose in 2 Gy fractions: a simple application of the linear quadratic formula. Int J Radiat Oncol Biol Phys 1995; 28: 335–341.
11. Ang K K, Price R E, Stephens L C et al. The tolerance of primate spinal cord to re-irradiation. Int J Radiat Oncol Biol Phys 1993; 25: 459–464.
12. Lee A, Poon Y, Foo W et al. Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976–1985: overall survival and patterns of failure. Int J Radiat Oncol Biol Phys 1992; 23: 261–267.
13. Hernandez-Linares W, Puthawala A, Nolan J F et al. Carcinoma in situ of the vagina: past and present management. Obstet Gynecol 1980; 56: 356–360.
14. Parsons J T, Bova F J, Fitzgerald C R, Mendenhall W M, Million R R. Radiation optic neuropathy after megavoltage external-beam irradiation: analysis of time dose factors. Int J Radiat Oncol Biol Phys 1994; 30: 755–763.

AUSTRALIAN CANCER STUDY QIMR COLLABORATION

1. Ibiebele TI, Hughes MC, Nagle CM, Bain CJ, Whiteman DC, Webb PM, et al. Dietary antioxidants and risk of Barrett's esophagus and adenocarcinoma of the esophagus in an Australian population. International Journal of Cancer. 2013;133(1):214-24.

2. Ibiebele TI, Hughes MC, Whiteman DC, Webb PM. Dietary patterns and risk of oesophageal cancers: a population-based case-control study. Br J Nutr. 2012;107(8):1207-16.

3. Pandeya N, Green AC, Whiteman DC. Prevalence and determinants of frequent gastroesophageal reflux symptoms in the Australian community. Dis Esophagus. 2012;25(7):573-83.

4. Thrift AP, Nagle CM, Fahey PP, Russell A, Smithers BM, Watson DI, et al. The influence of prediagnostic demographic and lifestyle factors on esophageal squamous cell carcinoma survival. Int J Cancer. 2012;131(5):E759-68.

5. Marwick Thomas H. When the Stomach Rules the Heart. Journal of the American College of Cardiology. 2011;58(15):1635-6.

6. Ibiebele TI, Taylor AR, Whiteman DC, van der Pols JC. Eating habits and risk of esophageal cancers: a population-based case-control study. Cancer Causes Control. 2010;21(9):1475-84.

7. Pandeya N, Webb PM, Sadeghi S, Green AC, Whiteman DC. Gastro-oesophageal reflux symptoms and the risks of oesophageal cancer: are the effects modified by smoking, NSAIDs or acid suppressants? Gut. 2010;59(1):31-8.

8. Doecke J, Zhao ZZ, Pandeya N, Sadeghi S, Stark M, Green AC, et al. Polymorphisms in MGMT and DNA repair genes and the risk of esophageal adenocarcinoma. Int J Cancer. 2008;123(1):174-80.

9. Whiteman DC, Parmar P, Fahey P, Moore SP, Stark M, Zhao ZZ, et al. Association of Helicobacter pylori infection with reduced risk for esophageal cancer is independent of environmental and genetic modifiers. Gastroenterology. 2010;139(1):73-83; quiz e11-2.

10. Sadeghi S, Bain CJ, Pandeya N, Webb PM, Green AC, Whiteman DC. Aspirin, Nonsteroidal Anti-inflammatory Drugs, and the Risks of Cancers of the Esophagus. Cancer Epidemiology Biomarkers & Prevention. 2008;17(5):1169.

11. Pandeya N, Williams GM, Sadhegi S, Green AC, Webb PM, Whiteman DC. Associations of duration, intensity, and quantity of smoking with adenocarcinoma and squamous cell carcinoma of the esophagus. Am J Epidemiol. 2008;168(1):105-14.

12. Whiteman DC, Sadeghi S, Pandeya N, Smithers BM, Gotley DC, Bain CJ, et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. Gut. 2008;57(2):173-80.

BJC British Journal of Cancer

www.nature.com/bjc

ARTICLE

Epidemiology

Dietary antioxidant intake and the risk of developing Barrett's oesophagus and oesophageal adenocarcinoma

James H-E Kang[1,2], Robert Luben[3], Leo Alexandre[1,2] and Andrew R Hart[1,2]

BACKGROUND: We investigated in a cohort study, for the first time using 7-day food diaries (7-DFDs), for age-dependent inverse associations with antioxidants, which have anti-carcinogenic properties, and development of Barrett's oesophagus (BO) and oesophageal adenocarcinoma (OAC).

METHODS: A total of 24,068 well individuals completed 7-DFDs and donated blood. Vitamins C and E, carotenes, zinc and selenium intakes, and plasma vitamin C were measured. Participants were monitored for 15 years for BO and OAC. Hazard ratios (HRs) were estimated for: quintiles of intake and in participants younger and >=65 years at recruitment, the midpoint of BO peak prevalence.

RESULTS: A total of 197 participants developed BO and 74 OAC. There were no significant associations between antioxidants and BO or OAC in the whole cohort or if >65 years at recruitment. In participants <65 years, for BO, there was an inverse trend across plasma vitamin C quintiles (trend HR = 0.82; 95% CI = 0.71–0.96, $P = 0.01$), OAC for plasma vitamin C (trend HR = 0.58; 95% CI = 0.37–0.92, $P = 0.02$) and for dietary vitamins C and E (trend HR = 0.71 95% CI = 0.51–0.99, $P = 0.04$ and trend HR = 0.70; 95% CI = 0.51–0.96; $P = 0.03$).

CONCLUSIONS: Data supports a role for dietary antioxidants prevent BO and OAC, perhaps at the earlier stages of carcinogenesis.

British Journal of Cancer (2018) 118:1658–1661; https://doi.org/10.1038/s41416-018-0113-y

INTRODUCTION

The aetiology of both Barrett's oesophagus (BO) and oesophageal adenocarcinoma (OAC), and the exposures that influence the malignant transformation of BO, is not fully understood. The carcinogenic processes may involve oxidative stress, whereby electrons are removed from: DNA, cellular proteins and membrane lipids.[1,2] Dietary antioxidants, including vitamins C and E, beta-carotene, selenium and zinc may inhibit oxidation and protect against BO and OAC. For BO, results from epidemiological studies investigating these dietary micronutrients are inconsistent.[3–7] Conversely, for OAC observational work consistently documents inverse associations with high-dietary antioxidant intakes.[3,6–11] A meta-analysis of eight case-control studies of OAC reported such associations for the highest vs lowest quartiles of vitamin C (OR = 0.49, 95% CI = 0.39–0.62), beta-carotene (OR = 0.46, 95% CI = 0.36–0.59) and vitamin E (OR = 0.80, 95% CI = 0.63–1.03).[9] However, all included studies were case-control investigations prone to both recall and selection biases. Furthermore, nutritional intakes were measured with semi-quantitative food frequency questionnaires (FFQs), which are less accurate than seven-day food diaries (7-DFDs).

We conducted a prospective cohort study to estimate, with more precision than previous work by using food diaries, if there were inverse associations between dietary antioxidants and the development of BO and OAC in the same population. To suggest whether dietary antioxidants influence either the earlier, later or both stages of carcinogenesis, we investigated micronutrient intake and the subsequent development of OAC differentially above and below the age of 65 years at recruitment. This age is the midpoint of the age range 60–69 years, which is the peak prevalence of BO diagnoses[12] when at least metaplasia, with or without dysplasia is present. Demonstrating inverse associations with higher antioxidant intakes may support population-based dietary interventions to prevent this highly aggressive cancer and justify randomised controlled trials of antioxidants in inhibiting the malignant progression of BO to OAC.

METHODS

The cohort comprised 24,068 individuals, aged 40–79 years, in the European Prospective Investigation of Cancer-Norfolk (EPIC-Norfolk) study, recruited between 1993 and 1997. At recruitment participants completed questionnaires on: demography, habitual diet and lifestyle including smoking. Participants attended a baseline health check, conducted by a nurse, who took non-fasting blood samples and anthropometric measurements. The nurse explained the 7-DFD, the first day that was a 24-h recall of previous day's intake. Participants completed the remaining 6 days at home documenting their entire intake. This included: food types, portion sizes, brands, cooking methods and recipes in eight separate meal and snack times. The 7-DFDs were returned and nutritionists inputted the data into a computer program called DINER (Data Into Nutrients for Epidemiological Research).[13] Nutritionists matched each diary entry to one of 11,000 food

[1]Norfolk and Norwich University Hospital NHS Foundation Trust, Norwich NR4 7UY, UK; [2]Norwich Medical School, University of East Anglia, Norwich NR4 7UQ, UK and [3]Strangeways Research Laboratories, Wort's Causeway, Cambridge CB1 8RN, UK
Correspondence: J-E. Kang (jameshekang@gmail.com)

Received: 27 October 2017 Revised: 22 March 2018 Accepted: 17 April 2018
Published online: 21 May 2018

Table 1. Baseline characteristics of participants

	Non-cases ($n = 23,624$)	BO cases ($n = 197$)	OAC cases ($n = 74$)
Gender			
Male (*n*, %)	10, 865 (46.0%)	140 (71.1%)**	60 (81.1%)**
Age at recruitment (years, median, range)	58.8 (39.5–79.1)	60.4 (40.1–76.1)	66.9 (46.7–76.3)**
Age at diagnosis (years, median, range)	—	67.4 (47.0–91.0)	73.0 (47.0–91.0)
Time from recruitment to diagnosis (years, median, range) BMI (kg/m^2, mean, standard deviation)	—	13.1 (1.2–20.8)	6.2 (0.6–11.7)
Smoking status (*n*, %)	26.4 (3.9)	27.0 (3.5)*	27.1 (4.0)
Never smokers	10814 (46.2%)	64 (32.8%)**	20 (27.4%)**
Former smokers	9879 (42.2%)	106 (54.4%)**	43 (58.9%)*
Current smokers	2729 (11.7%)	25 (12.8%)	10 (13.7%)
Alcohol intake (units/wk, median, range)	3.5 (0.0–121.0)	5.5 (0.0–53.0)*	2.5 (0.0–44.0)
Energy intake (kcal, median, range)	1969.9 (632.7–5618.9)	2175.6 (826.9–4121.3)**	2094.4 (1053.6–3399.6)
Vitamin supplement use (yes, %)	9828 (41.6%)	79 (40.1%)	23 (31.1%)
Education level, i.e. formal qualifications (n, %)			
None	8615 (36.5%)	79 (40.1%)	32 (43.2%)
O-level or equivalent	2424 (10.3%)	15 (7.6%)	6 (8.1%)
A-level or equivalent	9500 (40.2%)	83 (42.1%)	27 (36.5%)
Higher degree	3069 (13.0%)	20 (10.2%)	9 (12.2%)
Nutrient intake from food diaries			
Vitamin C (mg/day, median, range)	76.4 (0–665.1)	68.8 (16.0–1152.4)	74.8 (6.3–175.4)
Vitamin E (mg/day, median, range)	9.5 (0.3–74.5)	10.2 (1.3–32.5)*	9.5 (3.1–24.4)

*$P < 0.05$, **$P < 0.001$ between cases and controls

Table 2. Associations between quintiles of dietary antioxidant intake or plasma vitamin C and risk of BO

Nutrient intake from food diary (median, range)	Non-cases ($n = 23624$)	BO cases ($n = 197$)			
	n	*n*	HR[1] (95% CI)	HR[2] (95% CI)	HR[3] (95% CI)
Vitamin C (mg/day)					
Q1 (0– < 46.4)	4722	43	1.00	1.00	1.00
Q2 (46.4– < 65.8)	4720	44	1.01 (0.66–1.55)	0.83 (0.49–1.39)	1.64 (0.72–3.73)
Q3 (65.8– < 89.1)	4724	40	0.93 (0.60–1.45)	0.88 (0.53–1.47)	1.12 (0.46–2.70)
Q4 (89.1– < 123.3)	4730	34	0.81 (0.51–1.30)	0.73 (0.42–1.28)	1.12 (0.46–2.73)
Q5 (123.3–1152.4)	4728	36	0.79 (0.49–1.27)	0.57 (0.31–1.04)	1.53 (0.65–3.57)
P-value for trend across quintiles	—	—	0.18	0.07	0.66
Vitamin E (mg/day)					
Q1 (0.3– < 6.8)	4736	29	1.00	1.00	1.00
Q2 (6.8– < 8.6)	4733	31	0.93 (0.55–1.57)	1.09 (0.57–2.12)	0.68 (0.28–1.66)
Q3 (8.6– < 10.5)	4723	41	1.14 (0.69–1.87)	1.23 (0.65–2.29)	0.99 (0.43–2.28)
Q4 (10.5– < 13.3)	4721	43	1.18 (0.72–1.93)	0.89 (0.46–1.71)	1.89 (0.88–4.02)
Q5 (13.3–75.0)	4711	53	1.31 (0.80–2.12)	1.28 (0.69–2.35)	1.28 (0.55–2.96)
P-value for trend across quintiles	—	—	0.10	0.56	0.10
Plasma vitamin C (μmol/L)					
Q1 (3.0– < 37.0)	4287	43	1.00	1.00	1.00
Q2 (37.0– < 49.5)	4037	43	1.07 (0.69–1.64)	0.84 (0.51–1.39)	2.01 (0.82–4.89)
Q3 (49.5– < 58.7)	4156	38	0.98 (0.62–1.54)	0.77 (0.45–1.32)	1.86 (0.75–4.60)
Q4 (58.7– < 69.1)	4363	24	0.72 (0.43–1.21)	0.50 (0.26–0.95)	1.67 (0.64–4.36)
Q5 (69.1–242.0)	3924	23	0.74 (0.42–1.31)	0.48 (0.23–1.01)	1.82 (0.66–4.99)
P-value for trend across quintiles	—	—	0.15	0.01	0.37

HR[1], HR[2] and HR[3] adjusted for gender, recruitment age, smoking status, BMI, alcohol, energy intake (kcal), vitamin supplement usage and educational level (no formal qualifications/O-level/A-level/higher degree or equivalents) in: [1]whole cohort, [2] participants younger and [3]older than 65 years old at recruitment, respectively

Table 3. Associations between quintiles of dietary antioxidants and risk of OAC

Nutrient intake from food diary (min-max)	Non-cases ($n = 23624$)	OAC cases ($n = 73$)			
	n	*n*	HR^1 (95% CI)	HR^2 (95% CI)	HR^3 (95% CI)
Vitamin C (mg/day)					
Q1 (0– < 46.4)	4722	12	1.00	1.00	1.00
Q2 (46.4– < 65.8)	4720	20	2.02 (0.94–4.32)	1.43 (0.50–4.06)	2.85 (0.90–8.97)
Q3 (65.8– < 89.1)	4724	14	1.50 (0.66–3.45)	0.49 (0.12–2.00)	3.09 (0.97–9.77)
Q4 (89.1– < 123.3)	4730	13	1.35 (0.58–3.18)	0.35 (0.07–1.78)	2.82 (0.87–9.12)
Q5 (123.3–1152.4)	4728	14	1.64 (0.72–3.75)	0.36 (0.07–1.83)	3.60 (1.14–11.24)
P-value for trend across quintiles	—	—	0.57	0.04	0.06
Vitamin E (mg/day)					
Q1 (0.3– < 6.8)	4736	15	1.00	1.00	1.00
Q2 (6.8– < 8.6)	4733	14	0.92 (0.44–1.91)	0.33 (0.09–1.24)	1.63 (0.63–4.23)
Q3 (8.6– < 10.5)	4723	18	1.00 (0.49–2.05)	0.39 (0.11–1.32)	1.70 (0.66–4.35)
Q4 (10.5– < 13.3)	4721	13	0.79 (0.37–1.70)	0.32 (0.09–1.13)	1.38 (0.51–3.78)
Q5 (13.3–75.0)	4711	13	0.67 (0.30–1.48)	0.20 (0.49–0.80)	1.35 (0.49–3.72)
P-value for trend across quintiles	—	—	0.10	0.03	0.80
Plasma vitamin C (µmol/L)					
Q1 (3.0– < 37.0)	4287	19	1.00	1.00	1.00
Q2 (37.0– < 49.5)	4037	13	0.89 (0.42–1.86)	0.38 (0.10–1.39)	1.54 (0.59–4.03)
Q3 (49.5– < 58.7)	4156	20	1.62 (0.84–3.14)	0.42 (0.11–1.59)	3.16 (1.33–7.49)
Q4 (58.7– < 69.1)	4363	6	0.61 (0.24–1.57)	0.30 (0.06–1.45)	0.99 (0.29–3.35)
Q5 (69.1–242.0)	3924	6	0.85 (0.32–2.25)	(no cases)	2.08 (0.69–6.27)
P-value for trend across quintiles	—	—	0.59	0.02	0.25

HR^1, HR^2 and HR^3 adjusted for gender, recruitment age, smoking status, BMI, alcohol, energy intake (kcal), vitamin supplement usage and educational level (no formal qualifications/O-level/A-level/higher degree or equivalents) in: [1]whole cohort, [2]participants younger and [3]older than 65 years old at recruitment, respectively

items and 55,000 portion sizes within DINER, which best described it. DINER facilitated translation of participant-reported food consumption into structured nutrient data. Each 7-DFD had an average of 220 individual food and drink items reported. From this process, the daily intakes of vitamins C and E, zinc, selenium and carotenes were calculated. Plasma vitamin C was measured as a marker of bioavailability and intake. The cohort was monitored up 30 June 2015 to identify participants who developed either incident BO or OAC. Case notes were reviewed by clinical gastroenterologists, and to be included cases needed both endoscopic and histological verification.

In the analysis, micronutrients intakes from 7-DFDs and plasma vitamin C concentrations were divided into quintiles. There were 23,624 non-cases from the cohort, who had had their 7-DFDs coded. Cox proportional hazards models estimated hazard ratios (HRs) for developing BO or OAC separately for quintiles of antioxidants and plasma vitamin C. Analyses were adjusted for covariates of recruitment age and gender, and in a second model additionally body mass index (BMI), smoking, alcohol, energy intake, vitamin supplements and educational level. Analyses were repeated for participants younger and older than 65 years at recruitment, the mean of the reported midpoint of age range of BO.[12,14] We performed tests for linear trend across quintile categories of intake.

RESULTS

During follow-up, 197 participants were diagnosed with BO and 74 for OAC, with data from 23,624 non-cases available (Table 1). Metaplasia was classed as either: intestinal 69%, gastric 10%, mosaic 10% and not reported 11%. In total, 5% of participants had dysplasia and 7% subsequently developed OAC. In the multivariable analyses of participants in the whole cohort (91% completed all 7 days of the diary), there were no statistically significant associations between any quintile of dietary vitamin C, vitamin E, zinc, selenium or carotenes, and the risk of either BO or OAC, and no trends across any quintiles (Tables 2 and 3, data on zinc, selenium and carotenes not shown. Similarly, there were no such associations when these analyses were repeated for participants older than 65 years at recruitment. However, in participants younger than 65 years at recruitment who developed BO, statistically non-significant inverse associations were observed between all quintiles of both food diary assessed and plasma vitamin C (highest vs lowest quintile of dietary vitamin C HR = 0.57, 95% CI = 0.31–1.04, $P = 0.07$; highest vs lowest quintile of plasma vitamin C HR = 0.48, 95% CI = 0.23–1.01, $P = 0.06$), with a significant inverse trend across quintiles for plasma vitamin C and BO risk (trend HR = 0.82; 95% CI = 0.71–0.96; $P = 0.01$). There were no associations in this younger age group with any of the other dietary antioxidants. For OAC, participants recruited younger than 65 years, there were non-significant inverse associations for all quintiles of both dietary and plasma vitamin C (highest vs lowest quintile of dietary vitamin C HR = 0.36, 95% CI = 0.07–1.83, $P = 0.22$; highest vs lowest quintile of plasma vitamin C HR = 0.30, 95% CI = 0.06–1.45, $P = 0.14$), with significant inverse trends across quintiles for both dietary vitamin C intake (trend HR = 0.71; 95% CI = 0.51–0.99; $P = 0.04$) and plasma vitamin C (trend HR = 0.58; 95% CI = 0.37–0.92; $P = 0.02$). In this younger age group, there was a significant inverse association across quintiles of vitamin E intake and OAC (trend HR = 0.70; 95% CI = 0.51–0.96; $P = 0.03$), but no associations for quintiles or trends of either zinc, selenium or carotenes.

DISCUSSION

The main findings of this observational study were large inverse associations between both dietary and plasma vitamin C, dietary vitamin E and the risk of OAC, plus plasma vitamin C and BO, in participants at recruitment aged younger, but not older than, 65 years. Some evidence these associations may be protective ones are: plausible biological mechanisms for antioxidants preventing BO and OAC, large effect sizes, a biological gradient, associations persisting after correcting for confounders and temporality of dietary data collection, although to infer causality the findings need to be replicated in similar aetiological studies. The reasons for the inverse association between vitamins C and E and OAC in participants recruited younger than 65 years, the midpoint of the peak prevalence of symptomatically diagnosed BO, but not those older than 65 years, are uncertain. The molecular mechanisms for OAC involve metaplasia, dysplasia and malignant change. Our findings of inverse associations in participants recruited before the peak prevalence of BO and then the subsequent development of OAC is consistent with the hypothesis that pro-oxidation is involved in the earlier, rather than later histological changes in the oesophageal mucosa, which may be attenuated by dietary antioxidants. This epidemiological finding would support any laboratory mechanistic information showing earlier stages of carcinogenesis involve pro-oxidation.

The study's strengths include its prospective design, which ensured that antioxidant intakes were assessed prior to symptoms, thereby reducing recall bias. A strength was the accuracy of the 7-day food diaries for measuring habitual dietary intake, which were validated against 16 day weighed records, the gold standard for dietary studies. For vitamin C intake, the Spearman correlation coefficient for 7-DFDs was 0.70 compared with 0.54 from FFQs,[15] hence the former attenuate measurement error for diet. Follow-up bias should be minimal, as 20 years after EPIC recruitment, 95.6% of the population still have Norfolk post codes. In any observational study there is always the possibility of residual confounding, namely other dietary variables associated with antioxidant intake, which truly influence disease risk. There were relatively small numbers of participants in quintiles of antioxidants, although further follow-up will accrue more cases to give greater statistical precision. We acknowledge that inverse associations for antioxidants and OAC in the younger age group may be due to chance, although full statistical significance was reported for vitamins C and E. Only one diary record and plasma sample were recorded at baseline, and some individuals' diets will alter due to illness and seasonal changes. However, as this is a prospective cohort design and measurement error is applicable to future cases and non-cases, effect sizes will be an under-estimate rather than spurious overestimates. Repeated measures of diet over time in a cohort study reported intake remained stable and was unlikely to change between quintile categories.[16]

No previous prospective cohort study, whose methodology reduces recall and selection biases, has investigated dietary antioxidants and the risk of developing both BO and OAC in the same population. Prospective data from our investigation suggests the inverse associations with certain antioxidants are more likely to be true ones, although confirmation from other cohort studies is required. Such data may support randomised controlled trials assessing if these micronutrients prevent the transformation of BO.

ACKNOWLEDGEMENTS

The authors thank the EPIC-Norfolk participants who took part in this study and their general practitioners.

AUTHOR CONTRIBUTIONS

All authors were involved in the study concept, design, analysis and interpretation of data, drafting and revision of the manuscript. J.H.-E.K. collected data on patients with BO and OAC. A.R.H. supervised this project.

ADDITIONAL INFORMATION

Ethical approval and consent to participate: Ethics approval, in accordance with the Declaration of Helsinki, was provided by the Norwich District Ethics Committee. Patient consent was obtained.

Funding: The Study was supported by The Medical Research Council (G1000143) and Cancer Research UK (C864/A14136).

Competing interests: The authors declare no competing interests.

REFERENCES

1. Spechler, S. J.., Fitzgerald, R. C.., Prasad, Ga.., & Wang, K. K.. History, molecular mechanisms, and endoscopic treatment of Barrett's esophagus. *Gastroenterology* **138**, 854–869 (2010).
2. Chen, X. Esophageal adenocarcinoma: a review and perspectives on the mechanism of carcinogenesis and chemoprevention. *Carcinogenesis* **22**, 1119–1129 (2001).
3. Veugelers, P. J., Porter, G. A, Guernsey, D. L., Casson, A. G. Obesity and lifestyle risk factors8 for gastroesophageal reflux disease, Barrett esophagus and esophageal adenocarcinoma. Dis. Esophagus. **19**, 321–328 (2006).
4. Jiao, K., Rugge, P. & Verstovsek, A. E.-S. Dietary intake of vegetables, folate, and antioxidants and the risk of Barrett's esophagus. *Cancer Causes Control* **24**, 1005–1014 (2013).
5. Kubo, A. et al. Dietary antioxidants, fruits and vegetables, and the risk of Barrett's esophagus. *Am. J. Gastroenterol.* **103**, 1614–1624 (2008).
6. Murphy S. J. et al. Dietary antioxidant and mineral intake in humans is associated with reduced risk of esophageal adenocarcinoma but not reflux esophagitis or Barrett' s esophagus. J. Nutr. **140**, 1757–1763 (2010).
7. Ibiebele T. I. et al. Dietary antioxidants and risk of Barrett's esophagus and adenocarcinoma of the esophagus in an Australian population. Int. J. Cancer. **133**, 214–224 (2013).
8. Moe, G. L., Kristal, A. R., Levine, D. S., Vaughan, T. L. & Reid, B. J. Waist-to-hip ratio, weight gain, and dietary and serum selenium are associated with DNA content flow cytometry in Barrett' s esophagus. *Nutr. Cancer* **36**, 7–13 (2000).
9. Kubo, A.., & Corley, D. A.. Meta-analysis of antioxidant intake and the risk of esophageal and gastric cardia adenocarcinoma. *Am. J. Gastroenterol.* **102**, 2323–2330 (2007).
10. Dong, L. M. et al. Dietary supplement use and risk of neoplastic progression in esophageal adenocarcinoma. *Nutr. Cancer* **60**, 39–48 (2008).
11. Carman, S. et al. Vitamin E intake and risk of esophageal and gastric cancers in the NIH-AARP Diet and Health Study. *Int. J. Cancer* **125**, 165–170 (2009).
12. Cameron, A. J. & Lomboy, C. T. Barrett's esophagus: age, prevalence, and extent of columnar epithelium. *Gastroenterology* **103**, 1241–1245 (1992).
13. Welch, A. A. et al. DINER (Data Into Nutrients for Epidemiological Research) - a new data-entry program for nutritional analysis in the EPIC-Norfolk cohort and the 7-day diary method. *Public Health Nutr.* **4**, 1253–1265 (2001).
14. Cameron, A. J., Zinsmeister, A. R., Ballard, D. J. & Carney, J. A. Prevalence of columnar-lined (Barrett's) esophagus. Comparison of population-based clinical and autopsy findings. *Gastroenterology* **99**, 918–922 (1990).
15. Bingham, S. et al. Validation of dietary assessment methods in the UK arm of EPIC using weighed records, and 24-hour urinary nitrogen and potassium and serum vitamin C and carotenoids as biomarkers. *Int. J. Epidemiol.* **26**, S137–S151 (1997).
16. Goldbohm, R. A. et al. Reproducibility of a food frequency questionnaire and satbility of dietary habits determined from five anually repeated measurements. *Eur. J. Clin. Nutr.* **49**, 420–429 (1995).

British Journal of Nutrition (2012), **107**, 1207–1216
doi:10.1017/S0007114511004247

Dietary patterns and risk of oesophageal cancers: a population-based case–control study

Torukiri I. Ibiebele[1]*, Maria Celia Hughes[2], David C. Whiteman[3] and Penelope M. Webb[1] for The Australian Cancer Study

[1]*Gynaecological Cancers Group, Queensland Institute of Medical Research, 300 Herston Road, Herston, Brisbane, QLD 4006, Australia*
[2]*Cancer and Population Studies Group, Queensland Institute of Medical Research, 300 Herston Road, Herston, Brisbane, QLD 4006, Australia*
[3]*Cancer Control Group, Queensland Institute of Medical Research, 300 Herston Road, Herston, Brisbane, QLD 4006, Australia*

(Submitted 8 February 2011 – Final revision received 23 June 2011 – Accepted 6 July 2011 – First published online 7 September 2011)

Abstract

Epidemiological studies investigating the association between dietary intake and oesophageal cancer have mostly focused on nutrients and food groups instead of dietary patterns. We conducted a population-based case–control study, which included 365 oesophageal adenocarcinoma (OAC), 426 oesophagogastric junction adenocarcinoma (OGJAC) and 303 oesophageal squamous cell carcinoma (OSCC) cases, with frequency matched on age, sex and geographical location to 1580 controls. Data on demographic, lifestyle and dietary factors were collected using self-administered questionnaires. We used principal component analysis to derive three dietary patterns: 'meat and fat', 'pasta and pizza' and 'fruit and vegetable', and unconditional logistic regression models to estimate risks of OAC, OGJAC and OSCC associated with quartiles (Q) of dietary pattern scores. A high score on the meat-and-fat pattern was associated with increased risk of all three cancers: multivariable-adjusted OR 2·12 (95% CI 1·30, 3·46) for OAC; 1·88 (95% CI 1·21, 2·94) for OGJAC; 2·84 (95% CI 1·67, 4·83) for OSCC (P-trend $< 0·01$ for all three cancers). A high score on the pasta-and-pizza pattern was inversely associated with OSCC risk (OR 0·58, 95% CI 0·36, 0·96, P for trend=0·009); and a high score on the fruit-and-vegetable pattern was associated with a borderline significant decreased risk of OGJAC (OR for Q4 *v.* Q1 0·66, 95% CI 0·42, 1·04, P=0·07) and significantly decreased risk of OSCC (OR 0·41, 95% CI 0·24, 0·70, P for trend=0·002). High-fat dairy foods appeared to play a dominant role in the association between the meat-and-fat pattern and risk of OAC and OGJAC. Further investigation in prospective studies is needed to confirm these findings.

Key words: Dietary patterns: Oesophageal cancer: Case–control studies: Principal component analysis

Oesophageal cancer is the eighth most frequently diagnosed cancer and the sixth leading cause of cancer death worldwide, with an estimated 482 000 new cases and 407 000 deaths in 2008[1,2]. There are two histological types: adenocarcinoma which can occur in the oesophagus (OAC) or the oesophagogastric junction (OGJAC) and oesophageal squamous cell carcinoma (OSCC). The incidence of OAC has been increasing in Western countries[3] including Australia[4,5], with recent figures showing positive annual percentage changes of 4·2 and 4·3% in the incidence of OAC for men and women, respectively, in the two decades before 2005 in New South Wales, Australia[6]. These rapid changes in incidence prompted the present study.

Diet is a modifiable risk factor that may influence risk of cancers of the oesophagus[7–9]. The majority of epidemiological studies investigating the association between diet and cancer of the oesophagus have focused on individual nutrients[10–15], individual foods or food groups[10,15–23]; however, because of inconsistency among the results, the evidence for a role of diet in the aetiology of oesophageal cancer is not conclusive. Dietary pattern analysis has emerged in recent years as a way to shed more light on the role of diet in modifying disease risk. Unlike the individual nutrient or food group approach, the dietary pattern approach allows the study of foods as they are actually consumed, thus capturing the inter-correlations between foods and nutrients[24].

Abbreviations: OAC, oesophageal adenocarcinoma; OGJAC, oesophagogastric junction adenocarcinoma; OSCC, oesophageal squamous cell carcinoma; Q, quartile.

* **Corresponding author:** Dr T. I. Ibiebele, fax +61 7 3845 3503, email Torukiri.Ibiebele@qimr.edu.au

Few epidemiological studies have specifically investigated the association between dietary patterns and risk of OSCC[25–28], and only two have investigated OAC[25,29]. These previous studies have been relatively small in size (185 and 124 OAC cases), and results have been inconsistent. For example, while two studies[28,30] found an increased risk between a 'Western' or 'meat and fat' dietary pattern and the risk of OSCC, another reported a non-significantly decreased risk[25]. To further investigate the role of dietary patterns in OAC risk, we have used the information reported on a validated FFQ from a population-based case–control study to identify common food consumption patterns in Australia, and to relate these patterns to the risk of OAC, OGJAC and OSCC.

Materials and methods

Study design and participants

We used data from a nationwide case–control study of oesophageal cancer conducted in Australia, the details of which have been described elsewhere[31]. In summary, eligible case patients were people aged 18–79 years with a histologically confirmed primary invasive cancer of the oesophagus or oesophagogastric junction diagnosed between 1 July 2002 (1 July 2001, in Queensland) and 30 June 2005, in the mainland states of Australia. Patients were recruited through the major treatment centres and state-based cancer registries. A total of 1577 patients with oesophageal cancer were invited to participate in the study, of whom 1102 patients (858 through clinics and 244 through cancer registries) returned a completed questionnaire (70 % of those invited; 35 % of all patients diagnosed with incident oesophageal cancer during the study period). Details of the histological type and anatomical site of each tumour were abstracted from diagnostic pathology reports by medically qualified investigators. Tumour site was classified according to the WHO classification such that adenocarcinomas that straddled the junction of the oesophagus and stomach were called tumours of the oesophagogastric junction regardless of where the bulk of the tumour lay (OGJAC, ICD-O code 8140/3), while those located entirely above the oesophagogastric junction were considered oesophageal carcinomas[32]. Eight case patients were deemed ineligible on pathology review and excluded from the analysis, leaving 365 OAC, 426 OGJAC and 303 OSCC patients.

Potential controls were selected at random from the Australian Electoral Roll and frequency matched to the case series by age (5-year age groups), sex and state of residence. We aimed for similar numbers of male cases and controls in each stratum of age and state; female controls were intentionally oversampled at all ages to accommodate their simultaneous enrolment in a parallel study of ovarian cancer[33]. Of the 3258 potentially eligible control participants who were contacted and invited to participate, 216 were excluded (sixteen deceased, sixty-one were too ill, ninety-eight were unable to read or write in English and forty-one were unwilling to participate in the study). Of the 3042 remaining controls, 1580 returned the completed questionnaires (51 % of all potentially eligible controls contacted).

All study participants provided informed written consent. The study was approved by the human research ethics committees of the Queensland Institute of Medical Research and all participating institutions.

Exclusions and final sample size

Of the 1094 cases and 1580 controls who returned the main risk factor questionnaire, 199 participants (152 cases and 47 controls) had no opportunity to complete an FFQ because the nutrition component of the study commenced 6 months after the main study. A further thirty-five cases and five controls omitted responses to 10 % or more of FFQ items, while twenty-seven cases and twenty-one controls had implausible total energy intakes (<3360 or $>21\,000$ kJ for men and <2940 or $>16\,800$ kJ for women). The present analysis included 1507 (98 %) controls and 880 (93 %) cases: 299 with OAC, 336 with OGJAC and 245 with OSCC.

Non-dietary data

Data were collected via a self-administered questionnaire. Information was collected on age, education, smoking history, total lifetime alcohol consumption, use of aspirin or other non-steroidal anti-inflammatory drugs during the past 5 years, height and weight 1 year ago (1 year before diagnosis for cases), frequency of symptoms of gastro-oesophageal reflux, defined as the presence of heartburn ('a burning pain behind the breastbone after eating') or acid reflux ('a sour taste from acid or bile rising up into the mouth or throat') 10 years before diagnosis, and physical activity.

Dietary data and food grouping

Dietary data were obtained using a 139-item semi-quantitative FFQ, modified from the instrument developed by Willett *et al.*[34], and shown to be valid against weighed food records[35–37] and serum biomarkers[38], and reproducible[39] for use in Australia. Respondents recalled how often, on average, they consumed a standard serving size of a specific food item in the previous year (for controls) or in the year before their diagnosis (for cases) for 135 food items. Information on four additional items including the quantity of sugar habitually added to food or beverages and the discretionary use of fat as assessed by the frequency with which visible fat from meat, foods fried at home and fried take-away foods were consumed were obtained. We calculated daily food intake in g by multiplying the frequency of consumption per d by the standard serving size of each food as specified in the FFQ. The foods items were grouped into forty-four predefined food groups based on the similarity of nutrient profiles or culinary usage.

Dietary pattern derivation

Principal component analysis is a data reduction technique that reduces the number of observed variables by creating a small number of factors that account for much of the variance in the food groups[40,41]. We used the PROC FACTOR command in SAS (statistical software version 9.1; SAS Institute, Inc., Cary, NC, USA) to derive dietary patterns using the correlation matrix of the forty-four food groups among the combined group of cases and controls (Table S1, supplementary material for this article can be found at http://www.journals.cambridge.org/bjn). We considered eigenvalues > 1, screeplots and interpretability when determining the number of factors to be retained. The preliminary analysis yielded thirteen factors with eigenvalues > 1, which together accounted for 53% of the variance in the forty-four food groups. However, based on the point at which the screeplot of eigenvalues levelled off, we retained three factors that explained 25% of the total variance in the diet. To facilitate interpretability, the three factors were rotated using varimax rotation to obtain three dietary patterns that were orthogonal and uncorrelated with each other. Factor loadings were calculated for each food group and dietary pattern (Table 1). A positive loading for a food group indicates a direct association with the dietary pattern while a negative loading indicates that the food group contributes inversely to the dietary

Table 1. Factor loadings* for the relationship between food groups and factors representing dietary patterns in oesophageal cancer cases and controls

	Meat and fat	Pasta and pizza	Fruit and vegetable
Processed meat	0·67	–	–
Potato (high fat)	0·57	–	–
Discretionary fat	0·53	–	–
Red meat	0·50	–	–
High-fat dairy	0·48	–	–
White bread	0·48	–	–
Poultry (high fat)	0·46	–	–
Sweet snacks	0·46	–	–
Fat spread	0·43	−0·22	–
Ketchup/tomato sauce	0·40	–	–
Sweet drinks	0·39	–	–
Beer	0·36	–	−0·22
Savoury snacks	0·36	0·35	–
Low-fat dairy	−0·33	0·21	0·20
Eggs	0·31	–	0·21
Whole-meal bread	−0·30	0·24	0·34
Herbal and green tea	−0·29	0·34	–
Cream soup	0·25	–	0·23
Rice (brown)	−0·24	0·27	0·22
Pizza	0·23	0·52	–
Other fruits†	−0·22	–	0·64
Poultry (low fat)	−0·20	0·26	0·21
Legumes	–	0·28	0·31
Spirits	–	0·31	–
Wine	–	0·55	–
Other vegetables‡	–	–	0·59
Pasta	–	0·67	–
Pasta sauce (tomato-based)	–	0·64	–
Olives or pickled vegetables	–	0·49	–
Rice (white)	–	0·49	–
Salad dressing	–	0·45	0·26
Cereal products	–	0·44	0·26
Oily fish	–	0·34	0·35
Nuts	–	0·31	0·27
Green leafy vegetables	–	0·30	0·51
Other fish or seafood	–	0·29	0·29
Coffee	–	0·28	–
Fruit or vegetable juices	–	0·27	–
Fruits containing high vitamin C or A	–	–	0·60
Red or yellow vegetables	–	–	0·66
Cruciferous vegetables	–	–	0·54
Potato (low fat)	–	–	0·41
Breakfast cereal	–	–	0·39
Tea (black)	–	–	0·32
Vegemite§	–	–	0·21
Cumulative variance explained	11·7	8·2	5·5

* With orthogonal rotation, the factor loading scores are identical to the correlation coefficients; factor loadings with absolute values < 0·20 are not shown for clarity.
† Fruits other than those containing high levels of vitamin A or C.
‡ Vegetables other than red/yellow, leafy green or cruciferous vegetables.
§ An Australian spread made from yeast extract.

pattern. For each dietary pattern, a score was calculated for cases and controls by summing up the intake of each food group (in g) weighted by the factor loading of the food groups (Σ((food group$_i$ g/d) × (food group$_i$ factor loading)), where i = food group from 1 to 44)[42]. Factor scores for each pattern were then categorised into quartiles using the distribution of the population controls, for further analyses.

Statistical analysis

We used the χ^2 test to check for differences in proportions, and ANOVA to check for differences in the distribution of continuous variables across categories of potential risk factors. Unconditional logistic regression was used to calculate OR and 95 % CI as estimates of the relative risks of OAC, OGJAC and OSCC associated with quartiles of dietary pattern scores. We assessed linear trends by ranking factor scores from 1 to 4 (lowest to highest quartile) and modelling this as a continuous variable. We simultaneously adjusted for the potential confounding effects of factors shown to be associated with> oesophageal cancer in our previous studies[31,43,44]. These include age (years); sex (male, female); BMI 1 year previously (<25, 25·0–29·9, ≥30·0 kg/m^2); education (high school only, technical college or diploma, university); frequency of heartburn or acid reflux symptoms in the 10 years before diagnosis (never, <monthly, <weekly, >weekly, daily); pack-years of smoking (0, 1–14·9, 15–29·9, ≥30); average lifetime alcohol intake (never, <1–6, 7–20, ≥21 drinks/week); non-steroidal anti-inflammatory drugs use during the past 5 years (never, occasionally, less than weekly, at least weekly) and total energy intake (kJ; log-transformed). Further adjustment for state of residence and physical activity did not alter the effect estimates for the dietary patterns; hence these variables were not included in the final models.

Results

The three retained factors were labelled 'meat and fat', 'pasta and pizza' and 'fruit and vegetable' patterns, on the basis of the food groups with the highest factor loadings (Table 1). The meat-and-fat pattern was characterised by high positive loadings for processed meat, high-fat potato, discretionary fat, red meat, high-fat dairy, poultry with skin on, white bread, sweet snacks and fat spreads; and very low factor loadings for fruits, vegetables and fish. The pasta-and-pizza pattern featured high positive loadings for pasta, tomato-based pasta sauce, wine, pizza, olives or pickled vegetables, white rice and cereal products; and very low intakes of processed meat, high-fat potato, discretionary fat, red meat, and high-fat dairy. The fruit-and-vegetable pattern was characterised by high positive loadings for all types of fruits and vegetables, low-fat potatoes, breakfast cereals and wholemeal bread; and low factor loadings for processed meat, high-fat potato, discretionary fat, red meat, high-fat dairy and alcoholic beverages. Together, the three dietary patterns explained 25·4 % of the total variance in dietary intake (11·7 % for the meat-and-fat, 8·2 % for the pasta-and-pizza and 5·5 % for the fruit-and-vegetable patterns). Among control participants, intake of foods with positive factor loadings increased, and that of foods with negative factor loadings decreased monotonically with increasing dietary pattern score. Mean intake of foods with low factor loadings did not differ significantly across quartiles of dietary pattern scores (Table S2, supplementary material for this article can be found at http://www.journals.cambridge.org/bjn).

In general, cases were more likely to be older (≥50 years) and to be heavy smokers (≥30 pack-years) than controls. OAC and OGJAC cases were more likely to be male, obese and to experience symptoms of reflux (>1/month) than OSCC cases and controls, while OSCC cases were more likely to be heavy alcohol consumers (≥21 standard drinks/week) than OAC and OGJAC cases and controls (Table 2). In comparison with controls in the first quartile of the meat-and-fat dietary pattern, those in the fourth quartile were more likely to be male, more likely to be overweight or obese, more likely to smoke heavily (≥30 pack-years) or drink heavily (≥21 standard drinks/week). In contrast, compared with controls in the first quartile of the pasta-and-pizza pattern, those in the fourth quartile were younger, more likely to be female, more likely to have a university education, but less likely to smoke heavily. Compared with controls in the first quartile of the fruit-and-vegetable pattern, those in the fourth quartile were older, more likely to be females and less likely to smoke or drink heavily (Table 3).

A high score on the meat-and-fat dietary pattern was associated with increased risk of all three oesophageal cancers (OR 2·12, 95 % CI 1·30, 3·46, P for trend=0·002 for OAC; OR 1·88, 95 % CI 1·21, 2·94, P for trend=0·002 for OGJAC; OR 2·84, 95 % CI 1·67, 4·83, P for trend<0·0001 for OSCC; Table 4). A high score on the pasta-and-pizza pattern was associated with a decreased risk of OSCC only (OR 0·58, 95 % CI 0·36, 0·96, P-trend = 0·009), while high scores on the fruit-and-vegetable pattern were associated with a borderline significant decreased risk of OGJAC (OR 0·66, 95 % CI 0·41, 1·04) and a significantly decreased risk of OSCC (OR 0·41, 95 % CI 0·24, 0·70, P for trend=0·002). We found no association between the pasta-and-pizza or the fruit-and-vegetable dietary patterns and risk of OAC (Table 4).

We then considered whether the observed associations with the dietary patterns could be explained by individual food groups that contributed strongly to that pattern. For each pattern, we selected food groups with a loading ≥0·45 (or ≤ − 0·45) and added these one at a time to the model with the dietary pattern variable. Intake of high-fat dairy foods, a major contributor to the meat-and-fat pattern, was significantly associated with increased risk of both OAC and OGJAC. When we included both intake of high-fat dairy foods and the meat-and-fat dietary pattern score in the same model, the association between the meat-and-fat pattern and OAC was attenuated (the OR for quartile (Q) 4 *v.* Q1 fell from 2·12 to 1·69, 95 % CI 1·00, 2·86) and weaker than that for high-fat dairy foods (OR 2·46, 95 % CI 1·54, 3·94). A similar effect was seen for OGJAC where, in the joint model, there was a strong association with high-fat dairy foods (OR for Q4 *v.* Q1 = 1·83, 95 % CI 1·17, 2·86) and the association with the meat-and-fat pattern was weakened and non-significant

Table 2. Characteristics of cases and controls

(Numbers and percentages)

Characteristic	Controls (*n* 1507)	OAC (*n* 299)	OGJAC (*n* 336)	OSCC (*n* 245)	*P**
Age group (%)					
<50 years	17·8	8·4	8·9	6·9	
50–59 years	26·1	27·1	28·8	24·1	
60–69 years	33·6	35·8	33·5	34·7	
≥ 70 years	22·5	28·8	28·8	34·3	<0·0001
Sex (%)					
Male	66·1	90·6	85·8	60·0	
Female	33·9	9·4	14·2	40·0	<0·0001
BMI (%)					
< 25 kg/m^2	36·2	20·5	27·4	55·6	
25–29·9 kg/m^2	42·9	42·7	38·9	29·9	
≥ 30 kg/m^2	20·9	36·9	33·7	14·5	0·64
Education (%)					
High school only	40·9	46·5	37·7	57·1	
Technical/diploma	43·6	47·2	51·6	34·3	
University	15·5	6·4	10·7	8·6	<0·0001
Heartburn or acid reflux symptoms in previous 10 years (%)					
Never	43·1	21·8	28·9	45·9	
< 1/month	30·5	13·4	16·1	12·8	
1/month to <1/week	14·5	22·5	22·6	13·2	
Daily	11·9	42·3	32·4	28·1	<0·0001
Pack-years of smoking (%)					
Never smokers	44·7	25·1	24·3	23·1	
0–15	25·2	20·1	19·9	19·8	
15–29	13·2	19·1	22·3	20·2	
≥ 30	16·9	35·8	33·5	34·0	<0·0001
Alcohol intake, lifetime mean standard drinks per week (%)					
Non-drinkers	10·7	6·4	9·2	12·7	
< 1–6	38·0	27·5	29·7	26·6	
7–20	32·0	36·6	33·5	20·9	
≥ 21	19·3	29·5	27·6	39·8	<0·0001
Non-steroidal anti-inflammatory drug use (%)					
Never	43·7	46·3	47·6	51·5	
< 1/month	31·4	26·0	28·7	27·4	
< 1/week	9·7	8·8	9·3	7·9	
Weekly or more	15·2	18·9	14·4	13·4	0·08
Physical activity level (%)					
Low	19·3	23·8	21·7	29·5	
Moderate	41·0	36·6	37·7	30·7	
High	39·7	39·6	40·6	39·8	0·09

OAC, oesophageal adenocarcinoma; OGJAC, oesophagogastric junction adenocarcinoma; OSCC, oesophageal squamous cell carcinoma.

* From χ^2 test (sex) or χ^2 test for trend.

(the OR for Q4 *v.* Q1 fell from 1·88 to 1·54, 95 % CI 0·95, 2·48). None of the other high-loading food groups appreciably altered the association with the meat-and-fat pattern when included in the model. This suggests that the observed associations with the meat-and-fat pattern were due largely to the intake of high-fat dairy foods and perhaps not a true effect of the overall dietary pattern.

In contrast, while several food groups from each of the dietary patterns were significantly associated with OSCC risk, none appeared to account for a major portion of the associations between the dietary patterns and OSCC suggesting that these were true pattern effects.

When dietary patterns were derived separately for males and females, we observed factor loadings similar to those reported for the total population. We also found no evidence that the observed associations with dietary patterns were modified by BMI, reflux or smoking (data not shown).

Discussion

We identified three dietary patterns in this population-based case–control study, and together they explained 25 % of the variance in dietary intake as measured by an FFQ. The 'meat and fat' and 'fruit and vegetable' patterns were similar to those found previously in studies of ovarian cancer[45], and skin cancer[46] using a similar FFQ in an Australian population. Although it had a high positive factor loading for wine and a moderate positive factor loading for spirits, the 'pasta and pizza' pattern we observed differed from the 'alcohol' or 'drinker' dietary patterns described in other studies. Unlike the 'alcohol' and 'drinker' patterns, this pattern was not characterised by high positive factor loadings on beer, eggs, processed meat, red meat or discretionary fat; instead, it featured moderate loadings on oily fish, nuts, green leafy vegetables, non-oily fish and seafood.

Overall, our results showed that participants with high scores on the meat-and-fat dietary pattern had an almost

Table 3. Characteristics of 1507 control participants according to quartiles (Q) of dietary pattern score
(Numbers, percentages, mean values and standard deviations)

Characteristics of study controls	*n*	Meat-and-fat pattern					Pasta-and-pizza pattern					Fruit-and-vegetable pattern				
		Q1	Q2	Q3	Q4	*P**	Q1	Q2	Q3	Q4	*P**	Q1	Q2	Q3	Q4	*P**
Age (years)	1507															
Mean		61	61	60	59	0·02	66	63	59	55	<0·0001	56	60	61	64	<0·0001
SD		12	11	12	12		9	10	11	12		12	11	11	10	
Sex (%)																
Female	996	49·4	33·7	29·7	15·6	<0·0001	24·1	38·5	35·9	35·6	0·008	21·5	29·3	36·3	48·1	<0·0001
Male	511	50·6	66·3	70·3	84·4		75·9	61·5	64·1	64·4		78·5	70·7	63·7	51·9	
BMI (%)																
< 25 kg/m^2	541	43·6	35·6	30·5	32·9		37·1	31·5	37·7	38·2		39·1	33·5	34·8	37·5	
25–29·9 kg/m^2	642	39·5	45·9	43·7	43·0	<0·0001	42·4	43·3	42·2	43·8	0·15	40·5	45·3	44·2	41·6	0·80
≥ 30 kg/m^2	312	17·0	18·5	25·8	24·1		20·6	25·2	20·1	18·0		20·4	21·2	20·9	20·9	
Education (%)																
High school only	616	40·6	37·6	42·2	44·4		57·4	47·3	36·9	26·3		41·4	36·0	42·8	43·4	
Technical college	657	39·9	46·2	45·3	43·4	0·02	39·8	42·9	48·2	42·7	<0·0001	42·8	47·4	42·0	42·0	0·28
University	234	19·5	16·3	12·5	12·1		2·9	9·8	14·8	31·0		15·8	16·6	15·1	14·6	
Heartburn or acid reflux symptoms in previous 10 years (%)																
Never	649	46·7	41·6	40·3	43·1	0·006	43·8	43·4	43·0	42·2	0·03	47·0	39·6	42·0	43·9	0·08
< 1/month	460	33·3	33·0	26·1	28·1		24·4	27·3	32·4	36·3		30·1	33·2	33·9	24·7	
1/month to < 1/week	218	10·2	14·1	18·9	16·0		16·4	18·3	12·1	11·9		13·3	15·0	12·3	17·3	
Daily	180	9·8	11·2	14·7	12·9		15·4	10·9	12·6	9·6		9·7	12·2	11·8	14·1	
Pack-years of smoking (%)																
Never smokers	673	50·1	45·7	41·4	38·9	<0·0001	43·2	46·5	44·7	44·2	<0·0001	36·2	39·4	51·7	51·1	<0·0001
≤ 15	380	26·5	25·6	26·7	20·8		18·8	19·7	25·9	34·4		24·3	31·1	22·7	22·6	
15–29	199	10·9	15·3	11·4	16·0		11·1	15·3	13·8	12·4		15·5	12·2	11·5	13·8	
≥ 30	255	12·5	13·4	20·6	24·3		26·9	18·6	15·6	9·1		24·0	17·4	14·1	12·5	
Alcohol intake, lifetime mean standard drinks per week (%)†																
Non-drinkers	161	13·6	12·2	9·2	5·9	<0·0001	19·4	35·5	24·7	20·4	<0·0001	6·9	6·7	11·2	17·8	<0·0001
< 1–6	573	43·8	39·7	36·7	28·5		14·5	44·0	24·9	16·7		31·2	37·1	40·0	43·6	
7–20	482	28·6	33·7	31·7	35·1		8·5	39·7	33·4	18·3		35·4	35·8	31·3	25·5	
≥ 21	291	14·1	14·4	22·5	30·6		2·6	33·2	42·5	21·7		26·5	20·5	17·5	13·0	
Non-steroidal anti-inflammatory drug use (%)																
Never	657	46·7	43·5	43·6	39·7	0·04	48·3	46·2	42·8	39·0	0·61	45·4	41·5	43·7	44·5	0·04
Occasionally	472	29·6	33·2	32·5	30·3		25·4	29·9	34·8	34·2		33·7	32·1	31·7	28·3	
< weekly	145	9·8	8·7	9·2	11·5		7·1	6·9	11·1	12·7		10·6	12·7	8·9	6·4	
At least weekly	228	13·9	14·7	14·7	18·5		19·2	17·0	11·3	14·1		10·3	13·7	15·7	20·8	
Energy intake (kJ)	1507															
Mean		8130	8769	9551	11 389	<0·0001	8845	9094	9069	9941	<0·0001	7589	8531	9458	11 453	<0·0001
SD		2427	2404	2335	2616		2706	2793	2442	2709		2241	2128	2187	2582	

* From χ^2 test for trend (BMI, heartburn, smoking, alcohol, non-steroidal anti-inflammatory drugs use) or heterogeneity (sex, education) or ANOVA (age, energy intake).
† One standard drink = 10 g ethanol.

Table 4. Associations between dietary patterns and risk of oesophageal cancers
(Numbers, percentages, odds ratios and 95 % confidence intervals)

	Controls		OAC				OGJAC				OSCC			
Dietary pattern	*n*	%	*n*	%	OR	95 % CI*	*n*	%	OR	95 % CI*	*n*	%	OR	95 % CI*
Meat and fat														
Q1	434	29·1	42	14·6	1·00		55	16·9	1·00		53	23·6	1·00	
Q2	414	27·8	59	20·5	1·14	0·72, 1·80	63	19·4	0·94	0·62, 1·42	48	21·3	1·15	0·73, 1·82
Q3	357	24·0	80	27·8	1·25	0·79, 1·98	91	28·0	1·27	0·84, 1·91	55	24·4	1·64	1·03, 2·63
Q4	285	49·4	107	37·2	2·12	1·30, 3·46	116	35·7	1·88	1·21, 2·94	69	30·7	2·84	1·67, 4·83
P for trend			0·002				0·002				0·0001			
Pasta and pizza														
Q1	320	21·5	86	29·9	1·00		91	28·0	1·00		83	36·9	1·00	
Q2	363	24·4	73	25·4	0·99	0·67, 1·47	79	24·3	0·87	0·60, 1·26	61	27·1	0·72	0·48, 1·09
Q3	392	26·3	77	26·7	1·00	0·67, 1·50	72	22·2	0·77	0·52, 1·13	41	18·2	0·52	0·33, 0·83
Q4	415	27·6	52	18·1	0·72	0·45, 1·15	83	25·5	1·01	0·67, 1·52	40	17·8	0·58	0·36, 0·96
P for trend			0·25				0·82				0·009			
Fruit and vegetable†														
Q1	355	23·8	60	20·8	1·00		83	25·5	1·00		82	36·4	1·00	
Q2	382	25·6	81	28·1	1·26	0·84, 1·91	76	23·4	0·78	0·53, 1·14	47	20·9	0·57	0·37, 0·89
Q3	381	25·6	68	23·6	1·10	0·70, 1·74	89	27·4	0·92	0·62, 1·37	44	19·6	0·51	0·31, 0·83
Q4	372	25·0	79	27·4	1·29	0·77, 2·14	77	23·7	0·66	0·42, 1·04	52	23·1	0·41	0·24, 0·70
P for trend			0·49				0·16				0·002			

OAC, oesophageal adenocarcinoma; OGJAC, oesophagogastric junction adenocarcinoma; OSCC, oesophageal squamous cell carcinoma; Q, quartiles.
* OR adjusted for age (years); sex; education (school only, technical college or diploma, university); BMI 1 year ago (<25, 25·0–29·9, ≥30·0 kg/m^2); frequency of heartburn or acid reflux 10 years before diagnosis/recruitment (never, <monthly, <weekly, >weekly, daily); pack-years of smoking (0, 1–14·9, 15–29·9, ≥30); non-steroidal anti-inflammatory drugs use (never, occasionally, less than weekly, at least weekly); and total energy (kJ, log transformed).
† Additionally adjusted for lifetime alcohol intake (never, <1–6, 7–20, ≥21 drinks/week). The 'meat and fat' and 'pasta and pizza' patterns were not adjusted for alcohol as alcoholic drinks were high loading components of these patterns; however, additional adjustment for alcohol intake did not alter the results.

2-fold increased risks of OAC and OGJAC, and an almost 3-fold increased risk of OSCC. Participants with high scores on the pasta-and-pizza pattern had a 42 % decreased risk of OSCC, while those with high scores on the fruit-and-vegetable pattern had a borderline significant 34 % decreased risk of OGJAC and a significant 59 % decreased risk of OSCC.

Our finding of a positive association between the meat-and-fat pattern and OAC and OGJAC risks is consistent with the findings of a population-based case–control study from Sweden, where the authors reported a positive association between a high score on a 'Western' dietary pattern, similar to our 'meat and fat' dietary pattern, and risks of gastric cardia adenocarcinoma and OAC[25]. Our finding that this association was driven in part by consumption of high-fat dairy foods is consistent with reports from two population-based case–control studies in which positive associations were found between a high-fat dairy food group[23], or a high-milk dietary pattern[29] and risk of OAC. An inverse association between total intake of dairy products and risk of OAC has been reported however[29] and in our data, the low-fat dairy food group had a negative factor loading (−0·33) in relation to the meat-and-fat pattern, suggesting that participants whose diet followed the meat-and-fat dietary pattern were less likely to consume foods from the low-fat dairy food group. Taken together, it is therefore possible that the fat component of the high-fat dairy food group may be most important in contributing to increased OAC risk.

Our finding of a positive association between the meat-and-fat pattern and OSCC is consistent with findings from other case–control studies from Sweden[25], Uruguay[27] and Iran[28]. One mechanism postulated to explain this association is that processed meat contains high levels of nitrites and *N*-nitroso compounds which might exert a carcinogenic effect[11].

The inverse association we observed between the pasta-and-pizza dietary pattern and risk of OSCC warrants further exploration, given that this factor had a strong positive loading with wine, and the known strong links between alcohol intake and risk of OSCC. It is, however, consistent with our previous study that found a decreased OSCC risk among those with low to moderate intake of alcohol from wine (≤90 g/week)[43]. In the present analyses, the mean intake of alcohol from wine across all quartiles of the pasta-and-pizza pattern (8·8, 23·2, 45·5, 76·1 g/week) was below this level, indicating that this dietary pattern was characterised by modest wine consumption. In addition to wine, the pasta-and-pizza pattern featured moderate intakes of other foods such as green leafy vegetables, fruit and vegetable juices, nuts, legumes, oily fish and whole grains that contain micronutrients with known antioxidant and anticarcinogenic properties including flavonoids, folates, phytosterols, vitamins A, C, E and dietary fibre. Thus, several aspects of the pasta-and-pizza dietary pattern are similar to the 'Mediterranean diet' which has been shown to be associated with decreased risk of cancers of the upper aerodigestive tract[47].

Our finding of an inverse association between the fruit-and-vegetable dietary pattern and risk of OSCC is consistent with the findings of case–control studies from Uruguay[26,27] and Iran[28]. A Swedish study also found an inverse but non-significant association with a 'healthy' dietary pattern with components similar to our fruit-and-vegetable pattern[25]. The World Cancer Research Fund report states that there is evidence to support that fruits probably protect against oesophageal cancer[1]. A population-based case–control study[23], and a prospective study[21] reported inverse association between non-citrus fruits[23] or fruits in the Rosaceae botanical group[21]and decreased OSCC risk. The component of non-citrus fruits and fruits in the Rosaceae family from both studies are similar to 'other' fruits (fruits other than those containing high levels of vitamin C or A) in our study.

The strengths of our present study include its relatively large sample size, the population-based design and our ability to control for a large number of potentially important confounders. Also, ours is one of the few studies to investigate the association between dietary patterns and the three types of oesophageal cancer in the same study. A limitation is the low participation rate among controls and cases. Detailed information on the characteristics of non-participants are not available because of Australian privacy laws; nevertheless, comparison of our study control data to data from the Australian National Health Survey, a representative survey of the Australian adult population conducted in 2004 with a reported 90 % response rate[48], showed similar distributions of key characteristics including educational level, BMI and smoking (ever/never)[49]. The strong influence of current diet on recall of past diet raises concerns regarding the possibility of recall bias among cases if their diet changed as a result of their diagnosis, or because they experienced symptoms as a result of the presence of subclinical disease before diagnosis. To minimise this, study participants were asked to report recent changes to their diet in the last year or two. Exclusion of individuals who reported having changed their diet did not alter our findings. Another limitation is the use of FFQ, an instrument prone to measurement error in collecting dietary data; however, the FFQ from which the dietary patterns were derived has shown reasonably good validity when compared with weighed food records[36,37] and serum biomarkers[38]; and any non-differential measurement error is likely to have attenuated the associations that we have observed, thus strengthening the results of our present study. Finally, it is possible that our results could be biased if the association between dietary patterns and oesophageal cancer differs by tumour grade, a strong predictor of survival, and hence study participation. However, we found no evidence that the reported associations differed by tumour grade.

In conclusion, we have shown that a 'meat and fat' dietary pattern was associated with increased risks of OAC, OGJAC and OSCC, a 'pasta and pizza' pattern was inversely associated with OSCC risk, while a 'fruit and vegetable' pattern was associated with a decreased risk of OSCC and possibly OGJAC but not OAC. However, high-fat dairy foods appear to play a major role in the association between the meat-and-fat dietary pattern and oesophageal cancer. Further analyses using data from prospective studies would be valuable to confirm the role of dietary patterns in oesophageal cancer risk.

Acknowledgements

The Australia Cancer Study was supported by the National Health and Medical Research Council (NHMRC) of Australia (Program No.199600). P. M. W. is supported by a Research Fellowship from the NHMRC of Australia. D. C. W. is supported by a Future Fellowship from the Australian Research Council. The funding bodies played no role in the design or conduct of the study; the collection, management, analysis or interpretation of the data; or preparation, review or approval of the manuscript. T. I. I., M. C. H., D. C. W. and P. M. W. have no personal or financial conflicts of interest. D. C. W. and P. M. W. designed the study; T. I. I. and M. C. H. established the dietary databases, T. I. I. conducted the data analysis; T. I. I., D. C. W. and P. M. W. wrote the paper; and all authors read and approved the final manuscript.

The Australian Cancer Study

Investigators: David C. Whiteman MBBS, PhD, Penelope M. Webb MA, D Phil, Adele C. Green MBBS, PhD, Nicholas K. Hayward PhD, Peter G. Parsons PhD, David M. Purdie PhD.

Clinical collaborators: B. Mark Smithers FRACS, David Gotley FRACS PhD, Andrew Clouston FRACP PhD, Ian Brown FRACP.

Project Manager: Suzanne Moore RN, MPH.

Database: Karen Harrap BIT, Troy Sadkowski BIT.

Research Nurses: Suzanne O'Brien RN MPH, Ellen Minehan RN, Deborah Roffe RN, Sue O'Keefe RN, Suzanne Lipshut RN, Gabby Connor RN, Hayley Berry RN, Frances Walker RN, Teresa Barnes RN, Janine Thomas RN, Linda Terry RN MPH, Michael Connard BSc, Leanne Bowes BSc, MaryRose Malt RN, Jo White RN.

Clinical contributors:

Australian Capital Territory: Charles Mosse FRACS, Noel Tait FRACS.

New South Wales: Chris Bambach FRACS, Andrew Biankan FRACS, Roy Brancatisano FRACS, Max Coleman FRACS, Michael Cox FRACS, Stephen Deane FRACS, Gregory L. Falk FRACS, James Gallagher FRACS, Mike Hollands FRACS, Tom Hugh FRACS, David Hunt FRACS, John Jorgensen FRACS, Christopher Martin FRACS, Mark Richardson FRACS, Garrett Smith FRACS, Ross Smith FRACS, David Storey FRACS.

Queensland: John Avramovic FRACS, John Croese FRACP, Justin D'Arcy FRACS, Stephen Fairley FRACP, John Hansen FRACS, John Masson FRACP, Les Nathanson FRACS, Barry O'Loughlin FRACS, Leigh Rutherford FRACS, Richard Turner FRACS, Morgan Windsor FRACS.

South Australia: Justin Bessell FRACS, Peter Devitt FRACS, Glyn Jamieson FRACS, David Watson FRACS.

Victoria: Stephen Blamey FRACS, Alex Boussioutas FRACP, Richard Cade FRACS, Gary Crosthwaite FRACS, Ian Faragher FRACS, John Gribbin FRACS, Geoff Hebbard FRACP, George Kiroff FRACS, Bruce Mann FRACS, Bob Millar FRACS, Paul O'Brien FRACS, Robert Thomas FRACS, Simon Wood FRACS.

Western Australia: Steve Archer FRACS, Kingsley Faulkner FRACS, Jeff Hamdorf FRACS.

References

1. World Cancer Research Fund/American Institute for Cancer Research (2007) *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: AICR.
2. Jemal A, Center MM, DeSantis C, *et al.* (2010) Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev* **19**, 1893–1907.
3. Gallus S & La Vecchia C (2007) Is there a link between diet and esophageal cancer? *Nat Clin Pract Gastroenterol Hepatol* **4**, 2–3.
4. Lord RV, Law MG, Ward RL, *et al.* (1998) Rising incidence of oesophageal adenocarcinoma in men in Australia. *J Gastroenterol Hepatol* **13**, 356–362.
5. Thomas RJS, Lade S, Giles GG, *et al.* (1996) Incidence trends in oesophageal and proximal gastric carcinoma in Victoria. *Aust N Z J Surg* **66**, 271–275.
6. Stavrou EP, McElroy HJ, Baker DF, *et al.* (2009) Adenocarcinoma of the oesophagus: incidence and survival rates in New South Wales, 1972–2005. *Med J Aust* **191**, 310–314.
7. Ziegler RG (1991) Vegetables, fruits, and carotenoids and the risk of cancer. *Am J Clin Nutr* **53**, 251S–259S.
8. Chainani-Wu N (2002) Diet and oral, pharyngeal, and esophageal cancer. *Nutr Cancer* **44**, 104–126.
9. Donaldson MS (2004) Nutrition and cancer: a review of the evidence for an anti-cancer diet. *Nutr J* **20**, 19.
10. Tzonou A, Lipworth L, Garidou A, *et al.* (1996) Diet and risk of esophageal cancer by histologic type in a low-risk population. *Int J Cancer* **68**, 300–304.
11. Mayne ST, Risch HA, Dubrow R, *et al.* (2001) Nutrient intake and risk of subtypes of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev* **10**, 1055–1062.
12. Chen H, Tucker KL, Graubard BI, *et al.* (2002) Nutrient intakes and adenocarcinoma of the esophagus and distal stomach. *Nutr Cancer* **42**, 33–40.
13. Lu H, Cai L, Mu LN, *et al.* (2006) Dietary mineral and trace element intake and squamous cell carcinoma of the esophagus in a Chinese population. *Nutr Cancer* **55**, 63–70.
14. Wu AH, Tseng CC, Hankin J, *et al.* (2007) Fiber intake and risk of adenocarcinomas of the esophagus and stomach. *Cancer Causes Control* **18**, 713–722.
15. Park Y, Leitzmann MF, Subar AF, *et al.* (2009) Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. *Arch Intern Med* **169**, 391–401.
16. Brown LM, Swanson CA, Gridley G, *et al.* (1995) Adenocarcinoma of the esophagus: role of obesity and diet. *J Natl Cancer Inst* **87**, 104–109.
17. De Stefani E, Brennan P, Boffetta P, *et al.* (2000) Vegetables, fruits, related dietary antioxidants, and risk of squamous cell carcinoma of the esophagus: a case–control study in Uruguay. *Nutr Cancer* **38**, 23–29.
18. De Stefani E, Deneo-Pellegrini H, Ronco AL, *et al.* (2003) Food groups and risk of squamous cell carcinoma of the oesophagus: a case–control study in Uruguay. *Br J Cancer* **89**, 1209–1214.
19. Gonzalez CA, Pera G, Agudo A, *et al.* (2006) Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). *Int J Cancer* **118**, 2559–2566.
20. Yamaji T, Inoue M, Sasazuki S, *et al.* (2008) Fruit and vegetable consumption and squamous cell carcinoma of the esophagus in Japan: the JPHC study. *Int J Cancer* **123**, 1935–1940.

21. Freedman ND, Park Y, Subar AF, *et al.* (2007) Fruit and vegetable intake and esophageal cancer in a large prospective cohort study. *Int J Cancer* **121**, 2753–2760.
22. Gonzalez CA, Jakszyn P, Pera G, *et al.* (2006) Meat intake and risk of stomach and esophageal adenocarcinoma within the European Prospective Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* **98**, 345–354.
23. Navarro Silvera SA, Mayne ST, Risch H, *et al.* (2008) Food group intake and risk of subtypes of esophageal and gastric cancer. *Int J Cancer* **123**, 852–860.
24. Schwerin HS, Stanton JL, Smith JL, *et al.* (1982) Food, eating habits, and health: a further examination of the relationship between food eating patterns and nutritional health. *Am J Clin Nutr* **35**, 1319–1325.
25. Bahmanyar S & Ye W (2006) Dietary patterns and risk of squamous-cell carcinoma and adenocarcinoma of the esophagus and adenocarcinoma of the gastric cardia: a population-based case–control study in Sweden. *Nutr Cancer* **54**, 171–178.
26. De Stefani E, Boffetta P, Ronco AL, *et al.* (2008) Exploratory factor analysis of squamous cell carcinoma of the esophagus in Uruguay. *Nutr Cancer* **60**, 188–195.
27. De Stefani E, Deneo-Pellegrini H, Boffetta P, *et al.* (2009) Dietary patterns and risk of cancer: a factor analysis in Uruguay. *Int J Cancer* **124**, 1391–1397.
28. Hajizadeh B, Rashidkhani B, Rad AH, *et al.* (2010) Dietary patterns and risk of oesophageal squamous cell carcinoma: a case–control study. *Public Health Nutr* **13**, 1107–1112.
29. Chen H, Ward MH, Graubard BI, *et al.* (2002) Dietary patterns and adenocarcinoma of the esophagus and distal stomach. *Am J Clin Nutr* **75**, 137–144.
30. De Stefani E, Boffetta P, Fagundes RB, *et al.* (2008) Nutrient patterns and risk of squamous cell carcinoma of the esophagus: a factor analysis in Uruguay. *Anticancer Res* **28**, 2499–2506.
31. Whiteman DC, Sadeghi S, Pandeya N, *et al.* (2008) Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. *Gut* **57**, 173–180.
32. Spechler SJ, Dixon MF, Genta R, *et al.* (2000) Adenocarcinoma of the oesophago-gastric junction. In *World Health Organization Classiciation of Tumours: Pathology and Genetics of Tumours of the Digestive System* [SR Hamilton and LA Aaltonen, editors]. Lyon: IARC Press.
33. Olsen CM, Bain CJ, Jordan SJ, *et al.* (2007) Recreational physical activity and epithelial ovarian cancer: a case–control study, systematic review, and meta-analysis. *Cancer Epidemiol Biomarkers Prev* **16**, 2321–2330.
34. Willett W, Sampson L, Stampfer MJ, *et al.* (1985) Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* **122**, 51–65.
35. Ashton BA, Marks GC, Battistutta D, *et al.* (1996) Under reporting of energy intake in two methods of dietary assessment in the Nambour trial. *Aust J Nutr Diet* **53**, 53–60.
36. Marks GC, Hughes MC & van der Pols JC (2006) The effect of personal characteristics on the validity of nutrient intake estimates using a food-frequency questionnaire. *Public Health Nutr* **9**, 394–402.
37. Marks GC, Hughes MC & van der Pols JC (2006) Relative validity of food intake estimates using a food frequency questionnaire is associated with sex, age, and other personal characteristics. *J Nutr* **136**, 459–465.
38. McNaughton SA, Marks GC, Gaffney P, *et al.* (2005) Validation of a food-frequency questionnaire assessment of carotenoid and vitamin E intake using weighed food records and plasma biomarkers: the method of triads model. *Eur J Clin Nutr* **59**, 211–218.
39. Ibiebele TI, Parekh S, Mallitt KA, *et al.* (2009) Reproducibility of food and nutrient intake estimates using a semi-quantitative FFQ in Australian adults. *Public Health Nutr* **12**, 2359–2365.
40. Hatcher L (1994) *A Step-by-Step Approach to Using SAS for Factor Analysis and Structural Equation Modeling*. Cary, NC: SAS Publishing, SAS Institute, Inc.
41. Kubo A, Levin TR, Block G, *et al.* (2008) Dietary patterns and the risk of Barrett's esophagus. *Am J Epidemiol* **167**, 839–846.
42. Nettleton JA, Diez-Roux A, Jenny NS, *et al.* (2008) Dietary patterns, food groups, and telomere length in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Clin Nutr* **88**, 1405–1412.
43. Pandeya N, Williams G, Green AC, *et al.* (2009) Alcohol consumption and the risks of adenocarcinoma and squamous cell carcinoma of the esophagus. *Gastroenterology* **136**, 1215–1224, e1–e2.
44. Sadeghi S, Bain CJ, Pandeya N, *et al.* (2008) Aspirin, non-steroidal anti-inflammatory drugs, and the risks of cancers of the esophagus. *Cancer Epidemiol Biomarkers Prev* **17**, 1169–1178.
45. Kolahdooz F, Ibiebele TI, van der Pols JC, *et al.* (2009) Dietary patterns and ovarian cancer risk. *Am J Clin Nutr* **89**, 297–304.
46. Ibiebele TI, van der Pols JC, Hughes MC, *et al.* (2007) Dietary pattern in association with squamous cell carcinoma of the skin: a prospective study. *Am J Clin Nutr* **85**, 1401–1408.
47. Bosetti C, Gallus S, Trichopoulou A, *et al.* (2003) Influence of the Mediterranean diet on the risk of cancers of the upper aerodigestive tract. *Cancer Epidemiol Biomarkers Prev* **12**, 1091–1094.
48. Australian Bureau of Statistics (2006) National Health Survey: Summary of Results 2004–05 Vol. cat. no. 4364·0, Canberra.
49. Pandeya N, Williams GM, Green AC, *et al.* (2009) Do low control response rates always affect the findings? Assessment of smoking and obesity in two Australian case–control studies of cancer. *Aust N Z Public Health* **33**, 312–319.

doi:10.1111/j.1440-1746.2011.06726.x

GASTROENTEROLOGY

Prevalence and determinants of *Helicobacter pylori* sero-positivity in the Australian adult community

Nirmala Pandeya*,† and David C Whiteman† for the Australian Cancer Study

*School of Population Health, the University of Queensland, and †Queensland Institute of Medical Research, Royal Brisbane Hospital, Herston, Queensland, Australia

Key words
epidemiology < gastroenterology, *Helicobacter pylori* < gastroenterology, seroprevalence.

Accepted for publication 16 March 2011.

Correspondence
Dr Nirmala Pandeya, School of Population Health, The University of Queensland, Level2, Public Health Building, Herston Road, Herston, QLD 4006, Australia. Email: n.pandeya1@uq.edu.au

Abstract

Background and Aim: To estimate the sero-prevalence of *Helicobacter Pylori* infection in the Australian adult population and identify determinants.

Methods: We analyzed serum samples and questionnaire data from 1355 community controls who participated in a nationwide case-control study of esophageal cancer in Australia between 2002 and 2005. We estimated the prevalence ratio and 95% confidence interval using log binomial regression models.

Results: The age and sex standardized sero-prevalence of *H. pylori* was 15.5%. The prevalence of infection varied significantly with age, ranging from 5% (< 40 years) to 32% (≥ 70 years). *H. pylori* infection was significantly higher among those born overseas (prevalence ratio [PR] 1.63; 95% confidence interval [CI] 1.34–1.98) compared with those born in Australia or New Zealand. *H. pylori* sero-prevalence was 23% higher among participants living in the lowest quartile of socio-economic areas (PR 0.77; 95%CI 0.59–0.99 for Q4 compared with Q1). *H pylori* serostatus was significantly inversely associated with university education (PR 0.56; 95%CI 0.38–0.83), frequent reflux symptoms (PR 0.62; 95%CI 0.42–0.91), use of proton pump inhibitor (PR 0.69; 95%CI 0.48–0.98) and use of medications for gut spasms (PR 0.48; 95%CI 0.25–0.93). *H. pylori* serostatus was not associated with body mass index, smoking, alcohol or physical activity.

Conclusions: The prevalence of *H. pylori* infection in Australian adults is lower than other developed countries. *H. pylori* infection is most common among those living in the areas of socio-economic disadvantage or who were born overseas.

Introduction

Helicobacter Pylori is a Gram-negative microaerophilic bacterium that colonizes the gastric mucosa and damages the lining of the stomach. While the bacterium has also been causally linked with gastric cancer[1] and its eradication among symptomatic patients has been suggested to be an effective preventive measure,[2] the mechanisms through which *H. pylori* infection causes these conditions are not well understood. Moreover in developing countries where *H. pylori* infection is highly prevalent, many infected people never develop significant clinical symptoms or conditions. Meanwhile, recent studies have identified inverse associations between *H. pylori* infection and conditions such as gastro-esophageal reflux disease, Barrett's esophagus and esophageal adenocarcinoma,[3–5] consistent with the concept that this organism has evolved in close proximity with humans and may not be wholly deleterious.[6]

In recent years, studies have reported the prevalence of *H. pylori* infection in populations around the world.[7–11] These reports indicate that the prevalence of *H. pylori* is much higher in developing than developed countries, with up to 90% of the community members infected. In comparison, the prevalence is lower in developed countries such as the US (32%)[12] and European countries (51%).[13] Reported prevalence of *H. pylori* infection in Australia has varied from 15% to 38%.[14–17] The variation appears to be due to study design issues, including small sample sizes, geographic localization or restrictive participant selection criteria.[15,16] To date, only one large study has reported the population prevalence of *H. pylori* in Australia, and reported the lowest estimate so far among developed countries.[14]

In developed countries, the determining factors for higher prevalence of *H. pylori* infection have been age, gender,[18,19] lower socio economic status,[20] lower education level[21,22] and large family size.[23] Positive associations with high alcohol intake and smoking have also been reported by some studies[15,21,24,25] but not all.[19,26,27] Whether these same factors are determinants of *H. pylori* infection in the putatively low prevalence population of Australia is unclear.

Here, we describe the population prevalence of *H. pylori* infection in the Australian adult population and investigate the factors associated with infection.

Methods

We used blood samples and questionnaire data provided by community controls who took part in a nationwide case-control study of esophageal cancer in Australia between 2002 and 2005 inclusive. Full details of the study design and data collection have been published previously.[5,28] Briefly, participants (age 18–79 years) were randomly selected from the Australian Electoral Roll (enrolment is compulsory) matched to the esophageal cancer cases within strata of age (in 5-year age-groups), sex and state of residence. Of 3258 potentially eligible control participants who were contacted and invited to participate, 175 were excluded (16 died, 61 too ill to participate, 98 unable to read or write in English), and 41 were lost to follow up after initial contact. Of 3042 remaining controls, 1680 (55%) accepted the invitation and 1580 (51%) returned completed questionnaires. Facilities for the systematic collection of blood became available 6 months after the study commenced and no attempt was made to re-contact those participants who had already completed data collection. Hence, blood samples for *H. pylori* analysis were only available for 1400 control participants (46% of all potentially eligible controls contacted).

Following blood collection, serum samples were stored at –80°C and thawed immediately prior to testing. We used a rapid enzyme linked immunosorbent assay (ELISA) kit (Genesis Diagnostics Ltd, Littleport, Cambridge, UK) to detect immunoglobulin G (IgG) antibodies to *H. pylori* according to the manufacturer's instructions. Samples failing internal quality controls were re-tested up to three times. An index of < 0.9 was considered negative, an index of ≥ 1.1 was considered positive and values between 0.9 and 1.1 were equivocal. Participants with results in the equivocal range (< 3%) were excluded from the primary analyses. We also used self-reported demographic and lifestyle information provided by the controls to investigate the determinants of positive *H. pylori* infection.

We asked participants to report their level of education, general health, height and weight one year before participation, and their use of tobacco products and alcoholic beverages for discrete age intervals. Participants were also asked to report their frequency of use of aspirin/non-steroidal anti-inflammatory drugs (NSAIDs) during the past 5 years, use of medications for gastric and other conditions and their frequency of moderate and strenuous leisure-time physical activity. Participants also reported the frequency of gastro-esophageal reflux symptoms in the past year, defined as the presence of heartburn ("a burning pain behind the breastbone after eating") or acid reflux ("a sour taste from acid or bile rising up into the mouth or throat"). Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of height in meters. Physical activity index was calculated as low, moderate or high based on the self reported frequency and intensity of recreational activities at different age intervals.[29]

We used the Index of Relative Socio-economic Disadvantage, one of the four indices for Socio-Economic Index for Areas (SEIFA) defined by the Australian Bureau of Statistics[30] as a proxy measure for socio-economic status. SEIFA scores were assigned to the participants based on their residential postcode; in the population 80% of the scores are in the ranges from 880 to 1110.[30] They have been presented here in their quartiles (highest quartile referring to highest socio-economic condition) and also used as continuous variables in the multivariate model.

The study was approved by the research ethics committees of the Queensland Institute of Medical Research (QIMR) and collaborating institutions, and all participants gave informed consent to take part.

Statistical analysis

We aimed to estimate the prevalence of *H. pylori* infection in the Australian adult population and to investigate contributing factors based on the available self reported questionnaire data. As our controls were matched by age and sex to a national series of patients with esophageal cancer, we performed direct age standardization on our sample to estimate the prevalence of *H. pylori* infection in the Australian population.

To determine the significant contributing factors for *H. pylori* infection, we calculated the prevalence ratio (PR) and 95% confidence interval (95%CI), defined as the ratio of prevalence of *H. pylori* positivity in the exposed and non-exposed groups for the environmental and lifestyle factors under investigation. For cross-sectional studies with common outcomes, the PR provides an unbiased estimate of the risk ratio, and is superior to the odds ratio for this purpose.[31,32] To estimate the PR adjusted for other potentially confounding factors, we used log binomial regression models[33] for which the binary outcome was presence or absence of sero-positivity to *H. pylori* infection. We first performed crude analysis by comparing the distribution of *H. Pylori* infection among levels of demographic and lifestyle factors. In the second step, we included terms in the multivariate analysis model for age, sex and any factors that were statistically significant in the crude analysis. Exposures not significant in the univariate model were tested later for their possible significance and confounding effects, by adding them individually to the final model. We have presented results for the exposures that were included in the final multivariate model.

Results

Of the 1400 participants for whom blood samples were available for serological analysis, questionnaire information on demographic and lifestyle characteristics was available for 1355. Among them 302 (22.3%) tested positive and 1014 (74.8%) tested negative to *H. pylori* antibodies. The remaining 39 (2.9%) tested equivocal and were excluded from further analysis. The estimated prevalence of *H. pylori* infection, standardized by age and sex to the Australian population, was 15.5% (95%CI: 12%–19%). The prevalence varied significantly for different age groups, with the lowest prevalence observed among the youngest participants (~ 5% for < 40 years) compared to almost a third of those over 70 years old (31.6%) infected. The trend of increasing prevalence of *H. pylori* infection with age was statistically significant (P trend < 0.001). There was no significant difference in the observed prevalence between men (15.6%) and women (15.4%).

Helicobacter pylori infection was significantly more common among participants who were born overseas and the prevalence was highest among those born in Southern Europe (sample prevalence: 51%) (Table 1). Other factors associated with *H. pylori* infection on crude analysis were having two or more siblings, limited education and low household income. We observed

Table 1 Distribution of demographic characteristics of community controls with and without *Helicobacter pylori* positive serology in Australian Cancer Study (2002–2005)

Variable	*H. pylori* among controls		χ^2 *P*-value
	No *n* (%)	Yes *n* (%)	
Crude prevalence	1014 (77.0%)	302 (23.0%)	
Age (years)			
< 40	48 (4.7%)	3 (1.0%)	
40–49	144 (14.2%)	19 (6.3%)	
50–59	271 (26.7%)	64 (21.2%)	
60–69	345 (34.0%)	121 (40.1%)	
70+	206 (20.3%)	95 (31.5%)	*P* trend < 0.001
Sex			
Female	358 (35.3%)	92 (30.5%)	
Male	656 (64.7%)	210 (69.5%)	0.12
Country of birth			
Australia/New Zealand	809 (81.3%)	200 (67.6%)	
Western Europe, US, Canada	141 (14.2%)	60 (20.3%)	
Southern Europe	19 (1.9%)	20 (6.8%)	
Asia and Pacific	19 (1.9%)	10 (3.4%)	
South America and South Africa	7 (0.7%)	6 (2.0%)	< 0.001
Total number of siblings			
No sibling	56 (5.7%)	12 (4.1%)	
One sibling	205 (20.7%)	46 (15.5%)	
Two or more siblings	730 (73.6%)	238 (80.4%)	0.06
Total number of children			
One child	84 (9.6%)	21 (7.9%)	
Two or more children	787 (90.4%)	246 (92.1%)	0.38
Higher education			
None	380 (37.5%)	145 (48.0%)	
Technical college/Diploma	239 (23.6%)	59 (19.5%)	
Trade certificate/apprenticeship	220 (21.7%)	71 (23.5%)	
University degree	173 (17.1%)	27 (8.9%)	< 0.001
Household income			
< 15 000	108 (10.7%)	55 (18.2%)	
15–30 000	233 (23.0%)	87 (28.8%)	
30–45 000	154 (15.2%)	40 (13.2%)	
45–60 000	132 (13.0%)	28 (9.3%)	
60–80 000	103 (10.2%)	30 (9.9%)	
80–100 000	76 (7.5%)	13 (4.3%)	
100 000+	116 (11.4%)	19 (6.3%)	< 0.001
Not stated	92 (9.1%)	30 (9.9%)	
SEIFA score*			
Q1 (0–968)	222 (22%)	109 (36.2%)	
Q2 (968.1–1005)	271 (26.9%)	61 (20.3%)	
Q3 (1005.1–1059)	262 (26.0%)	65 (21.6%)	
Q4 (> 1059)	252 (25.0%)	66 (21.9%)	< 0.001

*Disadvantage score calculated from socio-economic index for areas (SEIFA) defined by Australian Bureau of Statistics using the post code area of living for each participant. Lower score represented areas with poor socio-economic status.

participants residing in areas with higher SEIFA scores (i.e. better economic indicator for the area) were less likely to have *H. pylori* infection than those residing in areas with lower SEIFA scores. In particular, those grouped in the first quartile of the score had significantly higher prevalence of *H. pylori* infection compared with the rest (Table 1). There was no difference in the prevalence of *H. pylori* between those with only one child and those having multiple children (Table 1).

Table 2 cross-tabulates *H. pylori* sero-status by lifestyle and environmental factors. The prevalence of *H. pylori* infection was significantly higher among smokers who smoked 30+ pack-years cigarettes in their lifetime and among ex-smokers than non-smokers. There was no difference in the prevalence of *H. pylori* infection between various levels of alcohol consumption, body mass index, physical activities index and aspirin or other NSAIDs use in this population. Those reporting frequent (at least weekly)

Table 2 Distribution of environmental and phenotypic characteristics of community controls with and without *Helicobacter pylori* positive serology in Australian Cancer Study (2002–2005)

Variable	*Helicobacter pylori* positivity among controls		χ^2 *P*-value
	No *n* (%)	Yes *n* (%)	
Smoking status			
Non-smoker	474 (47.1%)	125 (41.8%)	
Ex-smoker	404 (40.2%)	140 (46.8%)	
Current smoker	128 (12.7%)	34 (11.4%)	0.12
Total pack-years smoked			
Never smokers	474 (46.8%)	125 (41.4%)	
1–30 pack-years	386 (38.1%)	114 (37.8%)	
30+ pack-years	154 (15.2%)	63 (20.9%)	0.05
Average alcohol consumption			
None	106 (10.5%)	35 (11.6%)	
< 1 drinks/week	60 (5.9%)	23 (7.6%)	
1–6 drinks/week	309 (30.5%)	98 (32.6%)	
7–20 drinks/week	341 (33.7%)	86 (28.6%)	
21+ drinks/week	196 (19.4%)	59 (19.6%)	0.47
BMI last year			
< 24.9	356 (35.4%)	101 (33.8%)	
25–29.9	441 (43.8%)	132 (44.1%)	
30–34.9	144 (14.3%)	48 (16.1%)	
35+	66 (6.6%)	18 (6.0%)	0.86
Physical activity index			
Mild	209 (20.6%)	65 (21.7%)	
Moderate	406 (40.1%)	121 (40.3%)	
High	398 (39.3%)	114 (38.0%)	0.90
Heartburn or acid reflux in the past 12 months			
Never	432 (42.8%)	139 (46.3%)	
Less than weekly	443 (43.9%)	136 (45.3%)	
Weekly or more	135 (13.4%)	25 (8.3%)	0.06
Aspirin or other NSAID use			
Never	209 (20.6%)	57 (18.9%)	
Less than weekly	540 (53.3%)	155 (51.3%)	
Weekly or more	265 (26.1%)	90 (29.8%)	0.43
Used proton pump inhibitors (PPIs)			
Never	847 (85.0%)	268 (90.5%)	
Ever	149 (15.0%)	28 (9.5%)	0.02
Used H2 antagonists			
Never	802 (80.5%)	243 (82.1%)	
Ever	194 (19.5%)	53 (17.9%)	0.55
Taken medications for stomach cramp			
Never	920 (92.4%)	288 (97.3%)	
Ever	76 (7.6%)	8 (2.7%)	0.003
Prior history of abdominal surgery			
Never	859 (86.2%)	252 (85.1%)	
Ever	317 (13.8%)	44 (14.9%)	0.63
Self reported gastritis			
Never	898 (89.1%)	265 (88.6%)	
Ever	110 (10.9%)	34 (11.4%)	0.82
Self reported ulcer			
Never	891 (88.3%)	256 (85.3%)	
Ever	118 (11.7%)	44 (14.7%)	0.17

BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug.

Table 3 Results from the multivariate analysis of environmental and phenotypic characteristics of community controls with and without *Helicobacter pylori* positive serology in Australian Cancer Study (2002–2005)

Variable	Age sex only adjusted PR (95%CI)	Multivariate adjusted PR (95%CI)
Age		
Per 10 years increase	1.36 (1.23–1.51)	1.31 (1.18–1.45)
Sex		
Female	Reference	Reference
Male	1.05 (0.85–1.31)	1.06 (0.85–1.31)
Country of birth		
Australia/New Zealand	Reference	Reference
Western Europe, North America	1.42 (1.11, 1.81)	1.39 (1.10, 1.76)
Southern Europe	2.26 (1.66, 3.09)	1.92 (1.45, 2.54)
Asia and Pacific	1.92 (1.18, 3.13)	2.06 (1.28, 3.33)
Rest of the world	2.04 (1.13, 3.67)	2.97 (1.66, 5.33)
Number of siblings		
None	Reference	Reference
One	1.14 (0.65, 2.02)	1.20 (0.69, 2.09)
Two or more	1.56 (0.93, 2.62)	1.51 (0.91, 2.51)
SEIFA score*		
Q1 (0–968)	Reference	Reference
Q2 (968.1–1005)	0.62 (0.47, 0.81)	0.67 (0.51, 0.87)
Q3 (1005.1–1059)	0.64 (0.49, 0.84)	0.70 (0.53, 0.91)
Q4 (> 1059)	0.68 (0.52, 0.89)	0.77 (0.60, 0.99)
Higher education		
None	Reference	Reference
Trade certificate /apprenticeship	0.93 (0.73, 1.20)	0.95 (0.74, 1.22)
Technical college/Diploma	0.76 (0.58, 0.99)	0.83 (0.63, 1.09)
University degree	0.57 (0.39, 0.83)	0.58 (0.39, 0.86)
Heartburn or acid reflux past 12 month		
Never	Reference	Reference
Less than weekly	0.99 (0.81, 1.21)	1.09 (0.89, 1.32)
Weekly or more	0.62 (0.42, 0.92)	0.69 (0.47, 1.01)
Used proton pump inhibitors		
Never	Reference	Reference
Ever	0.58 (0.40, 0.83)	0.69 (0.48 , 0.98)
Medications for gut spasms		
Never	Reference	Reference
Ever	0.41 (0.21, 0.79)	0.48 (0.25, 0.93)

*Disadvantage score calculated from socio-economic index for areas (SEIFA) defined by Australian Bureau of Statistics using the post code area of living for each participant. Lower score represented areas with poor socio-economic status. CI, confidence interval; PR, prevalence ratio.

heartburn or acid reflux symptoms were less likely to be infected with *H. pylori.*

We also examined whether abdominal surgery, use of medications, or medical conditions such as gastritis or peptic ulcer were associated with *H. pylori* sero-positivity. Use of proton pump inhibitors (PPIs) and medications for stomach cramp were significantly more common among those with negative serology, but we observed no evidence of any associations between other medical gastric conditions or use of H_2 antagonists and *H. pylori* sero-positivity (Table 2).

Prevalence ratios for factors significantly associated with *H. pylori* infection are presented in Table 3, first with minimal adjustment (for age and sex only) and also with full adjustment for all significant explanatory factors. Age was a significant determinant of positive *H. pylori* infection, with a 28% increase in the prevalence for every 10 years increase in age after full adjustment. The association between *H. pylori* infection and smoking was not statistically significant and was thus not included in the final model. Country of birth was a significant predictor of infection with highest prevalence ratios observed for those born in Africa or South America followed by those born in the Asia/Pacific region. The prevalence of *H. pylori* decreased with increased SEIFA score with significantly higher prevalence among those at the first quartile of the score (Table 3). It was also higher among those with two or more siblings compared with none and approached statistical significance. The prevalence of *H. pylori* was 44% lower among university-educated participants compared to those with only school education, and was 38% lower among those reporting weekly reflux symptoms compared to those reporting no reflux symptoms. The prevalence of *H. pylori* sero-positivity remained significantly lower among users of PPIs or medications for gut spasms in the multivariate model (Table 3).

Discussion

In this study, we have estimated the prevalence of *H. pylori* in the Australian population and identified factors associated with seropositivity in a large, population-based sample. We observed significantly higher prevalence of *H. pylori* infection among those who were older, overseas born, with two or more siblings, and from disadvantaged backgrounds. We observed significantly lower prevalence of *H. pylori* infection among those who reported having frequent heartburn or acid reflux symptoms. This is also supported by our observation of significantly lower use of PPIs and medications for stomach cramps, which are positively associated with gastric acids. We did not observe significant differences in the prevalence of *H. pylori* infection in our study between men and women, or between people with different levels of smoking, alcohol consumption, body mass index or levels of physical activity.

The prevalence of *H. pylori* infection observed in this population was lower than that observed for other developed countries such as US,[12] UK[34] and other European countries[9,13] where it ranged from 30% to 60%. Our observation is, however, consistent with the previous report of 15% from a community based study conducted in Australia.[14] As observed, increasing prevalence of *H. pylori* with older age has been universal;[12,16,35,36] however, repeated cross-sectional studies of the same population have also observed successively lower prevalence among the same age groups of later birth cohorts[37–39] suggesting a birth cohort effect. It has been suggested that the *H. pylori* infection occurs mainly during childhood and that the rate of acquisition decreases with increasing age.[40] Hence, childhood living conditions and social environments are thought to play a significant role in the risk of infection at older ages. The decrease in the prevalence of infection among more recent generations is likely to be due to improved socio-economic condition and changed lifestyle that they have experienced during their formative years. In addition, the widespread exposure to antibiotics among younger generations of Australians may also have contributed to lower prevalence of *H. pylori*.

Our observation of higher prevalence ratios among migrants from the Asia-Pacific, South American or southern African countries is similar to previous findings of higher prevalence among migrants to other developed countries such as the Netherlands[41]and Switzerland.[42] Although we also observed an increase in the prevalence of infection for higher numbers of siblings as shown previously,[34] the significance of this association weakened after adjusting for country of birth and SEIFA score. Our data lacked the specific details on the number of people living in the respondent's household during childhood, and so our measure of number of siblings is only a proxy measure of living conditions at that time.

Our study has both strength and limitations. Strengths include the large sample size, the population-based sampling frame and the comprehensive health and lifestyle data that were collected systematically from all study participants. While previous studies have reported the prevalence of *H. pylori* in Australia, most were focused on subgroups of the population (e.g. restricted by location[16,17] or community[15,43]) and were not representative of the community at large. As a nationwide study, we captured variability between communities and provided an overall prevalence estimate for the adult Australian population. Our approach to analyzing the determinants of *H. pylori* infection differed from previous studies, in that we calculated prevalence ratios using a log binomial model instead of odds ratios. We did this because odds ratios tend to overestimate the risk ratio when the prevalence of exposure is high in cross-sectional studies. This approach also permitted us to control for confounding factors in our multivariate models.

Limitations of our study include the use of an antibody test to measure *H. pylori* infection. As antibody titer can attenuate over time, it may not be a perfect measure for past infection, especially among the elderly, because they would have more opportunity for early infection and then loss of titer. However, longitudinal studies investigating long term serostatus have found that most adults retain antibodies to *H. pylori* over long periods of time.[44] While our observation of stronger inverse associations with PPIs than reflux might suggest that participants with *H. pylori* are less likely to suffer chronic reflux, we cannot exclude the possibility that the effect might be due to *H. pylori* treatment among the symptomatic patients. Another limitation is the low response rate of 51% from the sampled population. As the non-respondents were more likely to reside in localities with lower socio-economic indices,[28] our estimate of prevalence of *H. pylori* may have been underestimated to some degree. To gauge the maximum effect such non-participation might confer on risk estimates, we conducted a sensitivity analysis in which we assumed that the prevalence of *H. pylori* infection was 50% higher among non-participants than participants, distributed by age, sex and SEIFA quartiles to the participants. (This pattern of distribution was necessary because while non-participation was higher among younger age groups, young age is negatively correlated with low infection prevalence. We therefore needed to consider both the positive and negative effects of non-participation on prevalence estimates). Even under this extreme scenario, we estimated the standardized prevalence of *H. pylori* infection in the adult Australian population to be no higher than 20%.

In conclusion, we have estimated the prevalence of *H. pylori* infection in Australia using a large population based sample and observed the lowest reported prevalence for developed countries. Age, country of birth, number of siblings, and low socio-economic status were significant predictors of *H. pylori* infection in this population, while heartburn and reflux were inversely associated with infection.

References

1 Uemura N, Okamoto S, Yamamoto S *et al*. *Helicobacter pylori* infection and the development of gastric cancer. *N. Engl. J. Med.* 2001; **345**: 784–9.
2 Fuccio L, Zagari RM, Eusebi LH *et al*. Meta-analysis: can *Helicobacter pylori* eradication treatment reduce the risk for gastric cancer? *Ann. Intern. Med.* 2009; **151**: 121–W32.
3 Loffeld R, van der Putten A. *Helicobacter pylori* and gastro-oesophageal reflux disease: a cross-sectional epidemiological study. *Neth. J. Med.* 2004; **62**: 188–91.
4 Islami F, Kamangar F. *Helicobacter pylori* and esophageal cancer risk: a meta-analysis. *Cancer Prev. Res.* 2008; **1**: 329–38.
5 Whiteman DC, Parmar P, Fahey P *et al*. Association of *Helicobacter pylori* infection with reduced risk for esophageal cancer is independent of environmental and genetic modifiers. *Gastroenterology* 2010; **139**: 73–83.

6 Blaser MJ. Disappearing microbiota: *Helicobacter pylori* protection against esophageal adenocarcinoma. *Cancer Prev. Res.* 2008; **1**: 308–11.
7 Fock KM, Ang TL. Epidemiology of *Helicobacter pylori* infection and gastric cancer in Asia. *J. Gastroenterol. Hepatol.* 2010; **25**: 479–86.
8 Cheng H, Hu FL, Zhang L *et al*. Prevalence of *Helicobacter pylori* infection and identification of risk factors in rural and urban Beijing, China. *Helicobacter* 2009; **14**: 128–33.
9 Ceballos FS, Samso CT, Alonso MG, Lopez CA, Soler LSD, Diaz-Rubio M. Prevalence of *Helicobacter pylori* infection in the healthy population of Madrid (Spain). *Rev. Esp. Enferm. Dig.* 2007; **99**: 497–501.
10 Malaty HM. Epidemiology of *Helicobacter pylori* infection. *Best Pract. Res. Clin. Gastroenterol.* 2007; **21**: 205–14.
11 Naja F, Kreiger N, Sullivan T. *Helicobacter pylori* infection in ontario: prevalence and risk factors. *Can. J. Gastroenterol.* 2007; **21**: 501–6.
12 Everhart JE, Kruszon-Moran D, Perez-Perez GI, Tralka TS, McQuillan G. Seroprevalence and ethnic differences in *Helicobacter pylori* infection among adults in the United States. *J. Infect. Dis.* 2000; **181**: 1359–63.
13 Gasbarrini G, Pretolani S, Bonvicini F *et al*. A population-based study of *Helicobacter pylori* infection in a European country—the san-marino study—relations with gastrointestinal-diseases. *Gut* 1995; **36**: 838–44.
14 Moujaber T, MacIntyre CR, Backhouse J, Gidding H, Quinn H, Gilbert GL. The seroepidemiology of *Helicobacter pylori* infection in Australia. *Int. J. Infect. Dis.* 2008; **12**: 500–4.
15 Lin SK, Lambert JR, Nicholson L, Lukito W, Wahlqvist M. Prevalence of *Helicobacter pylori* in a representative anglo-celtic population of urban Melbourne. *J. Gastroenterol. Hepatol.* 1998; **13**: 505–10.
16 Robertson MS, Cade JF, Savoia HF, Clancy RL. *Helicobacter pylori* infection in the Australian community: current prevalence and lack of association with abo blood groups. *Intern. Med. J.* 2003; **33**: 163–7.
17 Lam VWT, Trinh LK, Wilson RB. *Helicobacter pylori* infection and treatment outcome in an urban Australian population. *ANZ J. Surg.* 2006; **76**: 710–4.
18 de Martel C, Parsonnet J. *Helicobacter pylori* infection and gender: a meta-analysis of population-based prevalence surveys. *Dig. Dis. Sci.* 2006; **51**: 2292–301.
19 Murray LJ, McCrum EE, Evans AE, Bamford KB. Epidemiology of *Helicobacter pylori* infection among 4742 randomly selected subjects from Northern Ireland. *Int. J. Epidemiol.* 1997; **26**: 880–7.
20 Agreus L, Engstrand L, Svardsudd K, Nyren O, Tibblin G. *Helicobacter pylori* seropositivity among Swedish adults with and without abdominal symptoms—a population-based epidemiologic-study. *Scand. J. Gastroenterol.* 1995; **30**: 752–7.
21 Forman D, Debacker G, Elder J *et al*. Epidemiology of, and risk-factors for, *Helicobacter pylori* infection among 3194 asymptomatic subjects in 17 populations. *Gut* 1993; **34**: 1672–6.
22 Replogle ML, Glaser SL, Hiatt RA, Parsonnet J. Biologic Sex as a risk factor for *Helicobacter pylori* infection in healthy-young adults. *Am. J. Epidemiol.* 1995; **142**: 856–63.
23 Breuer T, Sudhop T, Hoch J, Sauerbruch T, Malfertheiner P. Prevalence of and risk factors for *Helicobacter pylori* infection in the western part of Germany. *Eur. J. Gastroenterol. Hepatol.* 1996; **8**: 47–52.
24 Fraser AG, Scragg R, Metcalf P, McCullough S, Yeates NJ. Prevalence of *Helicobacter pylori* infection in different ethnic groups in New Zealand children and adults. *Aust. N. Z. J. Med.* 1996; **26**: 646–51.
25 Bures J, Kopacova M, Koupil I *et al*. Epidemiology of *Helicobacter pylori* infection in the Czech republic. *Helicobacter* 2006; **11**: 56–65.
26 Russo A, Eboli M, Pizzetti P *et al*. Determinants of *Helicobacter pylori* seroprevalence among Italian blood donors. *Eur. J. Gastroenterol. Hepatol.* 1999; **11**: 867–73.
27 Moayyedi P, Axon AT, Feltbower R *et al*. Relation of adult lifestyle and socioeconomic factors to the prevalence of *Helicobacter pylori* infection. *Int. J. Epidemiol.* 2002; **31**: 624–31.
28 Pandeya N, Williams GM, Green AC, Webb PM, Whiteman DC. Do low control response rates always affect the findings? Assessments of smoking and obesity in two Australian case-control studies of cancer. *Aust. N. Z. J. Public Health* 2009; **33**: 312–19.
29 Olsen CM, Bain CJ, Jordan SJ *et al*. Recreational physical activity and epithelial ovarian cancer: a case-control study, systematic review, and meta-analysis. *Cancer Epidemiol. Biomarkers Prev.* 2007; **16**: 2321–30.
30 Australian Bureau of Statistics. *Socio-Economic Indexes for Areas Introduction, Use and Future Directions*. Canberra: Australian Bureau of Statistics, 2006.
31 Axelson O, Fredriksson M, Ekberg K. Use of the prevalence ratio V the prevalence odds ratio as a measure of risk in cross sectional studies. *Occup. Environ. Med.* 1994; **51**: 574.
32 Stromberg U. Prevalence odds ratio V prevalence ratio. *Occup. Environ. Med.* 1994; **51**: 143–4.
33 Blizzard L, Hosmer DW. Parameter estimation and goodness-of-fit in log binomial regression. *Biom. J.* 2006; **48**: 5–22.
34 Ford AC, Forman D, Bailey AG, Goodman KJ, Axon ATR, Moayyedi P. Effect of sibling number in the household and birth order on prevalence of *Helicobacter pylori*: a cross-sectional study. *Int. J. Epidemiol.* 2007; **36**: 1327–33.
35 Camargo MC, Lazcano-Ponce E, Torres J, Velasco-Mondragon E, Quiterio M, Correa P. Determinants of *Helicobacter pylori* seroprevalence in Mexican adolescents. *Helicobacter* 2004; **9**: 106–14.
36 Lane JA, Harvey RF, Murray LJ *et al*. A placebo-controlled randomized trial of eradication of *Helicobacter pylori* in the general population: study design and response rates of the bristol helicobacter project. *Control. Clin. Trials* 2002; **23**: 321–32.
37 Kumagai T, Malaty HM, Graham DY *et al*. Acquisition versus loss of *Helicobacter pylori* infection in Japan: results from an 8-year birth cohort study. *J. Infect. Dis.* 1998; **178**: 717–21.
38 Roosendaal R, Kuipers EJ, Buitenwerf J *et al*. *Helicobacter pylori* and the birth cohort effect: evidence of a continuous decrease of infection rates in childhood. *Am. J. Gastroenterol.* 1997; **92**: 1480–2.
39 Chen J, Bu XL, Wang QY, Hu PJ, Chen MH. Decreasing seroprevalence of *Helicobacter pylori* infection during 1993–2003 in Guangzhou, southern China. *Helicobacter* 2007; **12**: 164–9.
40 Sipponen P, Kosunen TU, Samloff IM, Heinonen OP, Siurala M. Rate of *Helicobacter pylori* acquisition among finnish adults—a 15-year follow-up. *Scand. J. Gastroenterol.* 1996; **31**: 229–32.
41 De Vries AC, Van Driel HF, Richardus JH *et al*. Migrant communities constitute a possible target population for primary prevention of *Helicobacter pylori* -related complications in low incidence countries. *Scand. J. Gastroenterol.* 2008; **43**: 403–9.
42 Heuberger F, Pantoflickova D, Gassner M *et al*. *Helicobacter pylori* infection in Swiss adolescents: prevalence and risk factors. *Eur. J. Gastroenterol. Hepatol.* 2003; **15**: 179–83.
43 Windsor HM, Abioye-Kuteyi EA, Leber JM, Morrow SD, Bulsara MK, Marshall BJ. Prevalence of *Helicobacter pylori* in indigenous Western Australians: comparison between urban and remote rural populations. *Med. J. Aust.* 2005; **182**: 210–3.
44 Rosenstock S, Jørgensen T, Andersen L, Bonnevie O. Seroconversion and seroreversion in igg antibodies to *Helicobacter pylori*: a serology based prospective cohort study. *J. Epidemiol. Community Health* 2000; **54**: 444–50.

IJC
International Journal of Cancer

The influence of prediagnostic demographic and lifestyle factors on esophageal squamous cell carcinoma survival

Aaron P. Thrift[1,2]*, Christina M. Nagle[1]*, Paul P. Fahey[1], Anne Russell[1], Bernard M. Smithers[3], David I. Watson[4] and David C. Whiteman[1]; for the Australian Cancer Study Clinical Follow-Up Study

[1] Population Health Department, Queensland Institute of Medical Research, 300 Herston Road, Brisbane, QLD, Australia

[2] School of Population Health, The University of Queensland, Public Health Building, Herston Road, Brisbane, QLD, Australia

[3] Department of Surgery, The University of Queensland, Upper Gastro-intestinal Unit, Princess Alexandra Hospital, Brisbane, QLD, Australia

[4] Department of Surgery, Flinders University, Adelaide, SA, Australia

Demographic and lifestyle factors, in particular tobacco smoking and alcohol, are well established causes of esophageal squamous cell carcinoma (ESCC); however, little is known about the effect of these factors on survival. We included all 301 patients with incident ESCC, recruited into a population-based case–control study of esophageal cancer in Australia. Detailed information about demographic and lifestyle factors was obtained at diagnosis, and deaths were identified using the National Death Index. Median follow-up for all-cause mortality was 6.4 years. Hazard ratios (HRs) and 95% confidence intervals (95% CI) were calculated from Cox proportional hazards models, adjusted for age, sex, pretreatment AJCC tumor stage, treatment and presence of comorbidities. Two hundred and thirteen patients (71%) died during follow-up. High lifetime alcohol consumption was independently associated with poor survival. Relative to life-long nondrinkers and those consuming <1 drink/week, the HRs for those with average consumption of 7–20 drinks/week or ≥21 drinks/week were 2.21 (95% CI = 1.27–3.84) and 2.08 (95% CI = 1.18–3.69), respectively. There was a suggestion of worse survival among current smokers (HR = 1.42, 95% CI = 0.89–2.28); however, the risk of early death was greatest among current smokers who reported regularly (≥7 drinks/week) consuming alcohol (HR = 3.84, 95% CI = 2.02–7.32). Other lifestyle factors putatively associated with risk of developing ESCC were not associated with survival. In addition to increasing disease risk, heavy alcohol consumption may be independently associated with worse survival among patients with ESCC. Future clinical follow-up studies should consider alcohol as a potential prognosticator, in addition to known clinicopathologic factors.

Esophageal cancer is the sixth leading cause of cancer mortality worldwide.[1] According to the most recent global estimates, cancers of the esophagus account for ~5% of all deaths (or 407,000 deaths) from cancer annually.[2] Moreover, as the majority of patients with esophageal cancer are diagnosed at an advanced stage, curative treatment is limited and

Members of the Australian Cancer Study Clinical Follow-Up Study: Investigators: D. C. Whiteman, A. C. Green, D. Gotley, B. M. Smithers, D. I. Watson, G. L. Falk, G. Smith, G. Kiroff, S. Archer, N. K. Hayward, A. Clouston. Project Managers: T. Corish, S. Moore. Database: K. Harrap, T. Sadkowski. Research Nurses: J. Thomas, E. Minehan, D. Roffe, S. O'Keefe, S. Lipshut, G. Connor, H. Berry, L. Terry, M. Connard, L. Bowes, M. R. Malt, J. White. Clinical Contributors: C. Mosse, N. Tait (Australian Capital Territory); C. Bambach, A. Biankan, R. Brancatisano, M. Coleman, M. Cox, S. Deane, J. Gallagher, M. Hollands, T. Hugh, D. Hunt, J. Jorgensen, C. Martin, M. Richardson, R. Smith, D. Storey (New South Wales); J. Avramovic, J. Croese, J. D'Arcy, S. Fairley, J. Hansen, J. Masson, I. Martin, L. Nathanson, B. O'Loughlin, L. Rutherford, R. Turner, M. Windsor (Queensland); J. Bessell, P. Devitt, G. Jamieson (South Australia); S. Blamey, A. Boussioutas, R. Cade, G. Crosthwaite, I. Faragher, J. Gribbin, G. Hebbard, B. Mann, B. Millar, P. O'Brien, R. Thomas, S. Wood (Victoria); K. Faulkner, J. Hamdorf (Western Australia).

Key words: alcohol, esophageal squamous cell carcinoma, lifestyle factors, survival, tobacco smoking

Abbreviations: AJCC: American Joint Committee on Cancer; BMI: body mass index; CI: confidence interval; EAC: esophageal adenocarcinoma; ESCC: esophageal squamous cell carcinoma; HR: hazard ratio; NDI: national death index; NSAIDs: nonsteroidal anti-inflammatory drugs

*A.P.T. and C.M.N. contributed equally to this work

Grant sponsor: Cancer Council Queensland; **Grant number:** Q129; **Grant sponsors:** National Health and Medical Research Council of Australia; **Grant number:** 199600, 389820, 552415; **Grant sponsors:** Cancer Council NSW; **Grant number:** SRP 08-04; **Grant sponsors:** Australia Research Council; **Grant number:** FT0990987; **Grant sponsors:** Australian Postgraduate Award (University of Queensland). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the funding bodies.

DOI: 10.1002/ijc.27420

History: Received 29 Aug 2011; Accepted 13 Dec 2011; Online 31 Dec 2011

Correspondence to: David C. Whiteman, Cancer Control Laboratory, Queensland Institute of Medical Research, Locked Bag 2000 Royal Brisbane Hospital, Queensland 4029, Australia, Tel: +61 7 3362 0279, Fax: +61 7 3845 3502, E-mail: david.whiteman@qimr.edu.au

overall prognosis is poor.[3] Despite advances in early diagnosis, and reduced risks associated with esophageal resection due to improved surgical techniques and perioperative treatments, the majority of patients will develop metastatic disease. Five-year survival is rarely greater than 20%.[1,3]

The two predominant histological subtypes of esophageal cancer, squamous cell carcinoma (ESCC) and adenocarcinoma (EAC), have very different patterns of incidence, reflecting their different etiologies.[4] Although ESCC incidence is decreasing in many Western countries,[4] it constitutes the majority of esophageal malignancies worldwide and still represents 90% of all esophageal cancer cases in most Asian, African and Eastern European countries.[5] The two main risk factors for ESCC are tobacco smoking and high alcohol consumption.[6,7] Well-conducted population-based studies have reported significantly increased risk of ESCC associated with smoking, regardless of dose.[7–9] According to a recent World Cancer Research Fund report,[10] alcohol is considered a "convincing" risk factor for esophageal cancer. Alcohol appears to have a threshold effect on ESCC,[6] with significantly increased risks observed with intakes above the maximum recommended US dietary guidelines (140 g/week).[11] Importantly, the joint effects of smoking and alcohol on the risk of ESCC appear to be multiplicative.[12] Social class is also associated with risk, with ESCC associated with low socioeconomic status.[13] In contrast, obesity,[9,14] high intakes of fruit and vegetables[15] and frequent use of aspirin or nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs)[16] have all been associated with reduced risks of ESCC.

Given the fundamental role of modifiable lifestyle factors in the etiology of ESCC, it is plausible that these factors may also have relevance to tumor behavior, progression and patient survival. Although stage and other clinical characteristics of the tumor are strongly related to prognosis,[3,17] only three previous studies have examined the role of demographic and lifestyle factors in survival.[17–19] Two of these studies followed-up patients who had originally participated in population-based case–control studies[17,18] and the other was a single institution study.[19] One study found no association with tobacco smoking, alcohol, body mass index (BMI) or use of NSAIDs,[17] another found that lean patients had better prognosis,[18] and two studies reported that smokers had poorer prognosis.[18,19] Demographic factors, including sex[17] and socioeconomic status,[18] were also associated with survival.

Here, we report findings from a large Australian population-based cohort of patients diagnosed with ESCC. We investigated the possible influence of prediagnostic lifestyle and demographic factors on ESCC survival in detail, with extensive adjustment for key clinical factors known to affect survival.

Material and Methods

Our study cohort was defined as all persons aged 18–79 years with a histologically confirmed incident diagnosis of ESCC ($n = 301$) who participated in a population-based case–control study conducted in mainland Australia. Full details of the original case–control study have been reported previously.[6] Briefly, patients with primary invasive esophageal cancer, diagnosed between 1 July 2001 and 30 June 2005, were recruited through major treatment centers and state-based cancer registries throughout Australia. A total of 1,577 patients with esophageal cancer received an invitation to participate in the study, of whom 1,102 patients returned a completed questionnaire (70% of all invited). Ten case patients were subsequently excluded following pathology review, and the final number of cases by histologic type was: 301 ESCC, 365 EAC and 426 gastroesophageal junction adenocarcinoma. Ethics approval for the research was received from the Queensland Institute of Medical Research and all the hospitals from where the participants were recruited. Written informed consent was obtained from all participants in the original study, which included granting the study investigators full access to their medical records.

Baseline data collection

On enrolment into the case–control study, all participants completed a health and lifestyle questionnaire asking about their education, occupation, general health, height, weight (at age 20, 1 year prior to diagnosis, and heaviest ever), past smoking history, past alcohol consumption and frequency of use of aspirin and nonaspirin NSAIDs in the 5 years prior to diagnosis. BMI at age 20, 1 year prior to diagnosis and heaviest ever was calculated by dividing weight (kg) by height squared (m^2), and standard World Health Organization categories were used for all analyses ($<$18.5 under weight; 18.5–24.9 healthy weight; 25.0–29.9 overweight; $\geq$30 obese). Participants were asked whether, over their whole life, they had ever smoked more than 100 cigarettes, cigars or pipes; positive responses elicited further questions about consumption and duration of smoking. Current smokers and ex-smokers were defined by their smoking status at 1 year prior to their diagnosis with ESCC.[7] Cumulative exposure to cigarettes in pack-years was calculated by multiplying the average number of cigarettes smoked per day by the number of years smoked and dividing by 20. We asked participants whether they currently drank alcohol, were life-long nondrinkers, or used to drink alcohol in the past but had stopped. For those who had ever consumed alcohol, we asked the age at which they first started drinking alcohol at least once a month and the age that they stopped drinking (if they had stopped). Participants then were asked to report the frequency with which they consumed alcohol (light beer, regular beer, white wine, red wine, port/sherry and spirits/liqueurs) at ages 20–29, 30–49 and $\geq$50 years, as applicable.[6] For these analyses, total alcohol consumption was summed across all the age groups for all types of alcohol, from which we calculated a weighted average number of standard drinks (10 g ethanol) consumed per week between age 20 and age at diagnosis. Life-long nondrinkers were similar to those who consumed $<$1 drink/week of alcohol, and so these groups were combined and used as the reference group for all analyses (four categories of

exposure: life-long nondrinkers (13% of the cohort) and <1 (6%); 1–6 (21%); 7–20 (20%); ≥21 (39%) drinks/week). Recent alcohol consumption was derived from the consumption of alcohol reported at the age interval coinciding with the participant's age at diagnosis with ESCC. Participants were also asked to report the presence of any medical conditions (from a predefined list) and/or any other medical conditions requiring regular medical care. These data were classified using the comorbidity categories defined by Charlson *et al.*,[20] and dichotomized (none or ≥1 comorbidities).

Clinical data collection

Clinical and pathologic information was abstracted from the medical records retrospectively by trained abstracters, entered on standardized data collection sheets, cleaned and checked. Information was collected regarding each patient's presenting symptoms, their diagnostic and staging investigations, the clinical stage of each patient's disease at diagnosis and their clinical management.[21] Pretreatment tumor stage (hereafter referred to as stage) was defined according to the American Joint Committee on Cancer (AJCC) stage groups for esophageal cancer.[22] As previously described,[21] for patients who did not have AJCC stage recorded in their medical notes we imputed AJCC stage using tumor-node-metastasis (TNM) codes, fluorodeoxyglucose positron emission tomography scan results for M status and endoscopic ultrasound for T and N status. However, for about half of the patients in this population sample, we were unable to impute AJCC stage with sufficient precision and so this group was classified separately as "AJCC stage undetermined." Tumor grade was defined as well differentiated, moderately differentiated or poorly/undifferentiated. Finally, we defined curative treatment intent as attempted resection and/or definitive chemoradiotherapy (*i.e.*, combined chemotherapy and radiotherapy where the radiotherapy was targeted at the esophagus and the dosage was 50 Gray or more).

Outcomes

All-cause mortality was the endpoint for follow-up. Personal identifiers were used to link the cohort to the National Death Index (NDI), which contains records on all deaths that have occurred in Australia since 1980. The NDI used probabilistic record linkage software that identified likely matches based on key identifiers (*e.g.*, full name, date of birth, sex, date of last known contact and state of residence of last contact). To identify a true match, we manually reviewed all potential matches identified by the NDI. Person-time was accumulated from a patient's date of consent to their date of death or to the date of last follow-up (15th September 2010). Median time from date of diagnosis to date of consent was 118 days. We had complete follow-up on mortality through the NDI, with the cohort followed for between 4.8 and 8.9 years from date of consent (median 6.4 years). Because the NDI has a lag time of more than 18 months for coded cause of death, we were able to obtain ICD-coded cause of death for only 133 of the 213 patients who had died (62%); most (91%) had died from esophageal cancer.

Statistical analysis

Overall and stratified survival distributions were estimated and plotted using the Kaplan-Meier technique, and log-rank tests were used to assess any heterogeneity in survival curves. Estimates of hazard ratios (HR) and 95% confidence intervals (95% CI) were obtained from Cox proportional hazards regression analysis. Terms for potential confounders were retained in the final models if they changed the β coefficient by 10% or more or improved the fit of the models. HR estimates for the demographic and lifestyle factors examined were adjusted for age, sex, AJCC stage (I, II, III, IV and undetermined), treatment and presence of comorbid conditions. Additional adjustment for other potential confounders (*e.g.*, tumor grade) did not significantly modify the reported HRs. To test for linear trends across categories, we modeled the median of each category as a continuous variable. For variables in which the lowest category was "unexposed" (*e.g.*, pack-years of smoking), trend tests were restricted to the "exposed" categories. Effect modification was assessed by examining stratum-specific estimates for prognostic factors, including age, AJCC stage and treatment. We evaluated the significance of interactions by assessing the p value for the type III analysis of effects for the interaction term. To assess biologic (additive)[23] interaction between alcohol and smoking, we created a new variable that reclassified patients according to their combined exposure. HRs for each category of combined exposure were estimated relative to the reference category in multivariate Cox regression analysis. We used the algorithm of Anderson *et al.*[24] to quantify biologic interaction by calculating the synergy index (SI).[23] Statistical significance was determined at $\alpha = 0.05$, and all tests for statistical significance were two-sided. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC).

Results

The distributions of patient characteristics at baseline are presented in Table 1. The majority of patients were male, and the median age was 66 years. Of those with tumor stage recorded, 54% were stages III and IV disease. For 87% of patients, tumor grade was poorly differentiated or moderately differentiated, in 42% of patients a resection was attempted, 65% of patients were treated with curative intent, and half had at least one comorbid condition. As expected, the majority consumed alcohol at least weekly on average over their lifetime (60%), were current or ex-smokers (75%), and were not overweight or obese (58%) prior to diagnosis.

A total of 213 patients (71%) died during follow-up. The overall 1- and 5-year survival rates were 67% (95% CI = 61–72) and 31% (95% CI = 26–36), respectively (Table 1). As expected, a significantly higher proportion of patients treated with curative intent or with earlier stage disease survived 1 and 5 years (Table 1). Surviving patients were also more likely to drink alcohol infrequently (less than weekly on average over their lifetime), more likely to have never smoked, and be female. The crude Kaplan-Meier survival curves by

Table 1. Baseline characteristics and the proportion of patients with ESCC who survived 1 and 5 years

Variables	Baseline n[1]	n (% survived at 1 yr)	1-year survivors *vs.* nonsurvivors p-value[2]	n (% survived at 5 yr)	5-year survivors *vs.* nonsurvivors p-value[2]
Total	301	201 (67)		93 (31)	
Sex					
Male	172	109 (63)		40 (23)	
Female	129	92 (71)	$p = 0.15$	53 (41)	$p < 0.001$
Age group					
<60 years	90	54 (60)		26 (29)	
60–69 years	106	74 (70)		32 (30)	
≥70 years	105	73 (70)	$p = 0.26$	35 (33)	$p = 0.75$
Highest level of education					
No tertiary qualification	173	123 (71)		53 (31)	
Technical College/Diploma	102	67 (66)		36 (35)	
University Degree	26	11 (42)	$p = 0.01$	4 (15)	$p = 0.13$
AJCC stage[3]					
I	15	13 (87)		5 (33)	
II	50	41 (82)		20 (40)	
III	43	27 (63)		9 (21)	
IV	35	16 (46)	$p = 0.002$	2 (6)	$p = 0.003$
Tumor grade					
Well differentiated	35	26 (74)		15 (43)	
Moderately differentiated	118	75 (64)		36 (31)	
Poorly/undifferentiated	120	81 (68)	$p = 0.48$	32 (27)	$p = 0.21$
Treatment intent					
Attempted resection and chemoradiotherapy	125	105 (84)		58 (46)	
Chemoradiotherapy only	71	49 (69)		23 (32)	
Noncurative intent	104	47 (45)	$p < 0.001$	12 (12)	$p < 0.001$
Number of comorbidities					
0	147	106 (72)		52 (35)	
≥1	154	95 (62)	$p = 0.06$	41 (27)	$p = 0.09$
Alcohol drinking status (1 year prior to diagnosis)					
Life-long nondrinker	39	33 (85)		23 (59)	
Ex-drinker	29	20 (69)		7 (24)	
Current drinker	233	148 (64)	$p = 0.04$	63 (27)	$p < 0.001$
Average lifetime alcohol consumption[4] **(standard drinks/week)**					
<1[5]	57	47 (82)		30 (53)	
1–6	63	45 (71)		22 (35)	
7–20	61	32 (52)		15 (25)	
≥21	117	74 (63)	$p = 0.004$	24 (21)	$p < 0.001$
Smoking status					
Never smoker	75	57 (76)		36 (48)	
Ex-smoker	132	83 (63)		37 (28)	
Current smoker	93	61 (66)	$p = 0.15$	20 (22)	$p < 0.001$
Cumulative smoking history					
Never smoker	75	57 (76)		36 (48)	
0–14.9 pack-years	59	35 (59)		16 (27)	

Table 1. Baseline characteristics and the proportion of patients with ESCC who survived 1 and 5 years (Continued)

Variables	Baseline n[1]	n (% survived at 1 yr)	1-year survivors *vs.* nonsurvivors p-value[2]	n (% survived at 5 yr)	5-year survivors *vs.* nonsurvivors p-value[2]
15.0–29.9 pack-years	55	35 (64)		18 (33)	
≥30 pack-years	111	73 (66)	$p = 0.20$	23 (21)	$p = 0.001$
BMI last year (kg/m^2)					
<18.5	14	7 (50)		5 (36)	
18.5–24.9	152	104 (68)		43 (28)	
25.0–29.9	78	52 (67)		28 (36)	
≥30.0	40	26 (65)	$p = 0.57$	14 (35)	$p = 0.62$
Frequency of use of NSAIDs in the 5 years prior to diagnosis					
Never	155	106 (68)		47 (30)	
Less than weekly	102	68 (67)		33 (32)	
At least weekly	35	22 (63)	$p = 0.81$	10 (29)	$p = 0.91$

AJCC: American Joint Committee on Cancer; BMI: body mass index; ESCC: esophageal squamous cell carcinoma; NSAIDs: nonsteroidal anti-inflammatory drugs.
[1]Numbers may not sum to total because of missing data. [2]p-value for χ^2 test for heterogeneity for comparing survivors to nonsurvivors for the distribution of each categorical variable. [3]One hundred and fifty-eight patients had undetermined pretreatment AJCC tumor stage (52%). [4]One standard drink is equivalent to 10 g of ethanol. [5]Includes life-long nondrinkers ($n = 39$) and patients consuming <1 drink/week on average of alcohol ($n = 18$).

AJCC tumor stage show that survival outcomes were poor among patients with late stage disease (log-rank $p < 0.0001$); however, among patients with AJCC stage undetermined the survival outcomes were similar to patients with AJCC stage 2 disease (Fig. 1*a*). As expected, in multivariate analyses, increasing AJCC tumor stage and noncurative treatment intent had clear adverse effects on survival (both p-trend <0.001; Table 2). Sex, age, tumor grade and the presence of comorbid conditions were not associated with survival in multivariate analyses.

The crude Kaplan-Meier survival curves in Figure 1*b* show worse survival among patients who reported a high average lifetime alcohol consumption (log-rank $p = 0.0001$). When included in the multivariate model alcohol remained a significant independent prognostic factor after adjusting for other clinicopathologic factors ($p = 0.04$); however, there was no trend of increasing risk across consumption categories (p-trend = 0.41; Table 3). We found that current drinkers (HR = 3.01, 95% CI = 1.64–5.54) and ex-drinkers (HR = 2.34, 95% CI = 1.14–4.83) had significantly worse survival compared to life-long nondrinkers. Compared to life-long nondrinkers and those consuming <1 drink/week on average, those who consumed on average 7–20 drinks/week or ≥21 drinks/week over their lifetime had HRs of 2.21 (95% CI = 1.27–3.84) and 2.08 (95% CI = 1.18–3.69), respectively. These effects were slightly attenuated but still significant when we restricted the comparison to recent alcohol consumption (7–20 drinks/week, HR = 1.80, 95% CI = 1.16–2.80; ≥21 drinks/week, HR = 1.57, 95% CI = 1.00–2.51). We observed a modest positive association between current smoking and survival (HR = 1.42, 95% CI = 0.89–2.28, $p = 0.15$); however, this was not statistically significant and there was no statistical evidence for a dose-response relation with increased cumulative exposure to cigarettes (p-trend = 0.82). We assessed the combined effects of alcohol and smoking by comparing risks of death among patients exposed to smoking, alcohol or both, compared to those exposed to neither (results not shown). Highest risk was observed among current smokers whose average alcohol consumption was ≥7 drinks/week (HR = 3.84, 95% CI = 2.02–7.32). However, we found no evidence that the HR associated with exposure to both alcohol and smoking was significantly different from that expected under the simple additive model (SI = 1.38, 95% CI = 0.43–4.75). We found no evidence that highest level of education, BMI or use of NSAIDs were associated with survival.

We repeated the multivariate analyses for alcohol consumption within strata of age, AJCC stage and treatment (surgical *vs.* nonsurgical; Table 4). Although the interaction terms between alcohol consumption and each of these factors were uniformly nonsignificant, the effect estimates for heavy drinking (≥21 drinks/week) associated with survival appeared greater among patients aged ≥60 years (HR = 2.78, 95% CI = 1.41–5.49), those with stage III/IV disease (HR = 2.35, 95% CI = 0.69–8.06) and patients who were not treated surgically (HR = 3.90, 95% CI = 1.75–8.72).

Discussion

We examined the associations between demographic and lifestyle factors and survival among a large cohort of patients with ESCC. As expected, we found that increasing AJCC tumor stage and noncurative treatment intent were strongly and adversely associated with survival. Of interest was our finding that alcohol consumption was associated with poor survival, independent of the effects of other prognostic factors. Other demographic and lifestyle factors reported to have

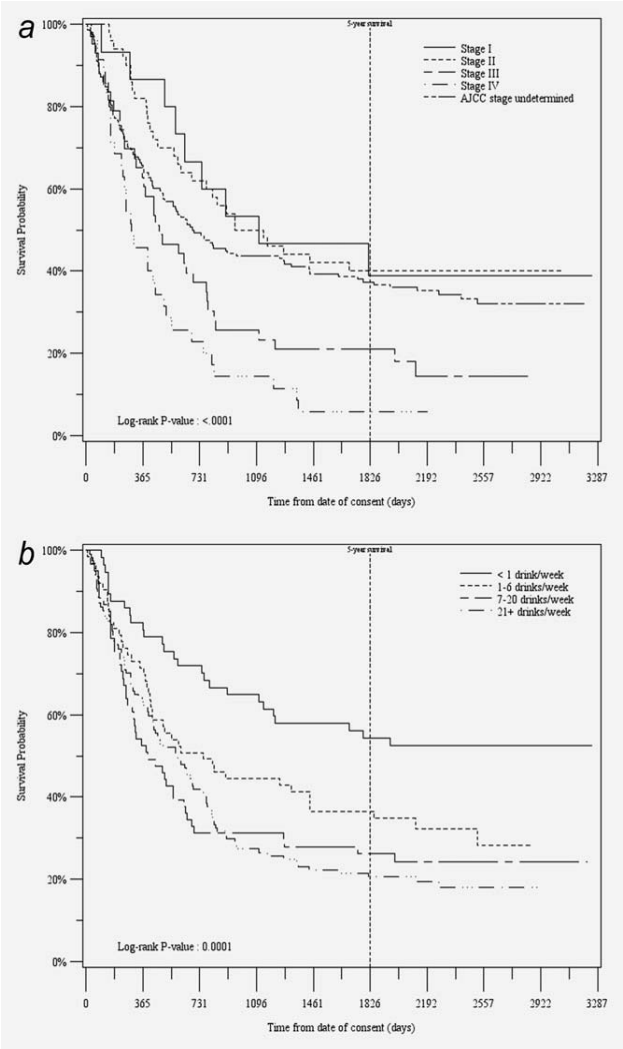


Figure 1. Kaplan-Meier survival curves by (*a*) pretreatment AJCC tumor stage and (*b*) average lifetime alcohol consumption for patients with ESCC.

Table 2. Crude and adjusted hazard ratios and 95% confidence intervals for the influence of sex, age and clinical factors on risk of death among patients with ESCC

Variables	Crude HR (95% CI)	Adjusted HR[1] (95% CI)
Sex		
Male	1.00	1.00
Female	0.62 (0.47–0.82)	0.75 (0.55–1.02)
Age in years (continuous)	1.00 (0.99–1.01)	0.99 (0.97–1.01)
Age group		
<60 years	1.00	1.00
60–69 years	0.92 (0.66–1.28)	0.74 (0.52–1.05)
≥70 years	0.87 (0.62–1.22)	0.71 (0.48–1.04)
AJCC stage		
I	1.00	1.00
II	1.05 (0.50–2.21)	1.23 (0.51–3.01)
III	2.07 (1.00–4.30)	2.52 (1.05–6.05)
IV	3.09 (1.48–6.49)	2.65 (1.07–6.57)
Undetermined[2]	1.36 (0.69–2.69)	1.86 (0.81–4.28)
Tumor grade		
Well differentiated	1.00	1.00
Moderately differentiated	1.44 (0.89–2.35)	1.56 (0.94–2.56)
Poorly/undifferentiated	1.44 (0.89–2.34)	1.31 (0.80–2.14)
Treatment intent		
Attempted resection and chemoradiotherapy	1.00	1.00
Chemoradiotherapy only	1.51 (1.05–2.18)	1.28 (0.86–1.90)
Noncurative intent	3.24 (2.36–4.44)	3.16 (2.24–4.45)
Number of comorbidities		
0	1.00	1.00
≥1	1.34 (1.02–1.75)	1.25 (0.92–1.68)

AJCC: American Joint Committee on Cancer; ESCC: esophageal squamous cell carcinoma; CI: confidence interval; HR: hazard ratio. [1]Mutually adjusted for all variables in the table. [2]Patients with AJCC stage undetermined were retained in multivariate models as a separate category.

etiologic relevance, including education level (a proxy for socioeconomic status), BMI, tobacco smoking and frequency of use of NSAIDs, were not independently associated with survival in this cohort.

To our knowledge, only two previous studies with similar aims and design (case–control follow-up studies)[17,18] and one recent single institution study[19] have examined the prognostic role of demographic and lifestyle factors among patients with ESCC. Analogous studies have reported that higher alcohol consumption and tobacco smoking were independent prognostic factors for patients with squamous cell cancers of the head and neck.[25,26] Heavy alcohol consumption (≥7 drinks/week) was independently associated with poorer survival in our cohort. In contrast, Sundelof *et al.*[18] found no association with average alcohol consumption 20 years prior to diagnosis (>70 g/week, HR = 0.6, 95% CI = 0.3–1.4), Shitara *et al.*[19] found no association with heavy consumption at diagnosis (≥5 days/week, 48 g/day or two standard Japanese alcoholic drinks), and Trivers *et al.*[17] found no association with ever consuming alcohol (≥1 alcoholic drink/month for ≥6 months). These contrasting findings may result from limited power due to smaller number of drinkers at higher levels in those previous studies (reflecting different consumption rates between the underlying populations) or differences in the alcohol exposure measurement. For example, the prevalence of regular drinkers (≥7 drinks/week on average) in our cohort (60%) was higher than in the Swedish cohort (47%).[18] Because these previous studies did not collect information on lifetime consumption, it is also possible that participants may have been misclassified with respect to lifetime alcohol exposure. Although misclassification is unlikely to be differential with respect to the outcome (death), patients with earlier onset disease may have drunk more alcohol in early life, and then reduced their intake in

Epidemiology

Table 3. Crude and adjusted hazard ratios and 95% confidence intervals for influence of demographic and lifestyle factors on risk of death among patients with ESCC

Variables	Crude HR (95% CI)	Adjusted HR[1] (95% CI)	*p*-trend
Alcohol drinking status (1 year prior to diagnosis)[2]			
Life-long nondrinker	1.00	1.00	
Ex-drinker	2.47 (1.30–4.71)	2.34 (1.14–4.83)	
Current drinker	2.59 (1.55–4.32)	3.01 (1.64–5.54)	
Average lifetime alcohol consumption[2,3] (standard drinks/week)			
<1[4]	1.00	1.00	
1–6	1.82 (1.12–2.94)	1.75 (1.02–2.99)	
7–20	2.45 (1.52–3.95)	2.21 (1.27–3.84)	
≥21	2.51 (1.63–3.85)	2.08 (1.18–3.69)	*0.41*
Smoking status[5]			
Never smoker	1.00	1.00	
Ex-smoker	1.88 (1.30–2.73)	1.15 (0.74–1.79)	
Current smoker	1.99 (1.34–2.95)	1.42 (0.89–2.28)	
Cumulative smoking history[5]			
Never smoker	1.00	1.00	
0–14.9 pack-years	2.07 (1.34–3.18)	1.44 (0.89–2.31)	
15.0–29.9 pack-years	1.66 (1.06–2.59)	0.99 (0.59–1.65)	
≥30 pack-years	2.01 (1.37–2.94)	1.26 (0.79–2.02)	*0.82*
Highest level of education			
No tertiary qualification	1.00	1.00	
Technical College/Diploma	0.92 (0.69–1.24)	0.99 (0.73–1.34)	
University Degree	1.81 (1.15–2.85)	1.27 (0.79–2.06)	
BMI last year (kg/m^2)			
<18.5	0.97 (0.49–1.92)	1.02 (0.50–2.07)	
18.5–24.9	1.00	1.00	
25.0–29.9	0.87 (0.63–1.20)	0.76 (0.54–1.06)	
≥30	0.85 (0.56–1.31)	0.99 (0.62–1.56)	*0.30*
Frequency of use of NSAIDs in the 5 years prior to diagnosis			
Never	1.00	1.00	
Less than weekly	0.94 (0.70–1.27)	1.00 (0.74–1.35)	
At least weekly	1.04 (0.67–1.62)	1.10 (0.70–1.72)	*0.58*

CI: confidence interval; ESCC: esophageal squamous cell carcinoma; HR: hazard ratio; NSAIDs: nonsteroidal anti-inflammatory drugs.
[1]Adjusted for age, sex, AJCC stage (I, II, III, IV and undetermined), treatment intent and presence of comorbidities. [2]Additionally adjusted for smoking status. [3]One standard drink is equivalent to 10 g of ethanol. [4]Referent group includes life-long nondrinkers and patients consuming <1 drink/week on average of alcohol. [5]Additionally adjusted for average lifetime alcohol consumption.

response to their symptoms. We assessed this in our cohort by considering both lifetime and recent alcohol consumption. In our cohort, patients reported higher levels of alcohol intake between ages 20–49 years than after 50 years. Although the associations with survival were attenuated, they remained significant for recent alcohol consumption. Lifetime consumption is arguably a more stable exposure measure than recent exposure, and these previous studies may have therefore underestimated the adverse effects of alcohol on survival from ESCC. Those at greatest risk in our study were current smokers who reported regularly (≥7 drinks/week) consuming alcohol. We found no evidence however of synergy between tobacco smoking and alcohol consumption.

Lean patients (defined as having BMI < 22 kg/m^2 20 years prior to diagnosis) and patients with high socioeconomic status (patients with higher education and/or high income) have been found to have better survival prospects among patients with ESCC in two earlier studies.[17,18] However, in our study, BMI 1 year prior to diagnosis was not an independent prognostic factor for ESCC. Although it is possible that BMI 1 year prior to diagnosis may underestimate a patient's BMI prior to onset of cancer symptoms, we found

Table 4. Adjusted hazard ratios and 95% confidence intervals for influence of alcohol consumption on risk of death among patients with ESCC, stratified by important prognostic factors

Average lifetime alcohol consumption[1] (standard drinks/week)	<1 drink/week[2] Adjusted HR[3] (95% CI)	1–6 drinks/week Adjusted HR[3] (95% CI)	7–20 drinks/week Adjusted HR[3] (95% CI)	≥ 21 drinks/week Adjusted HR[3] (95% CI)	*p*-trend
Age					
<60 years	1.00	0.87 (0.29–2.65)	2.02 (0.71–5.77)	1.37 (0.47–4.02)	$p = 0.81$
≥60 years	1.00	2.50 (1.34–4.66)	2.24 (1.15–4.37)	2.78 (1.41–5.49)	$p = 0.23$
(*p-interaction*)					($p = 0.10$)
AJCC Stage					
I-II	1.00	1.46 (0.49–4.36)	0.89 (0.28–2.82)	0.88 (0.29–2.71)	$p = 0.18$
III-IV	1.00	1.49 (0.42–5.30)	3.51 (0.99–12.5)	2.35 (0.69–8.06)	$p = 0.66$
Undetermined	1.00	2.46 (1.15–5.27)	2.58 (1.15–5.77)	3.04 (1.33–6.95)	$p = 0.19$
(*p-interaction*)					($p = 0.11$)
Treatment					
Surgery	1.00	0.91 (0.43–1.93)	1.43 (0.64–3.22)	1.09 (0.49–2.42)	$p = 0.94$
No surgery	1.00	3.79 (1.77–8.11)	3.65 (1.69–7.89)	3.90 (1.75–8.72)	$p = 0.21$
(*p-interaction*)					($p = 0.45$)

AJCC: American Joint Committee on Cancer; CI: confidence interval; ESCC: esophageal squamous cell carcinoma; HR: hazard ratio.
[1]One standard drink is equivalent to 10 g of ethanol. [2]Includes life-long nondrinkers and patients consuming <1 drink/week on average of alcohol.
[3]Adjusted for age, sex, AJCC stage (I, II, III, IV and undetermined), treatment intent, presence of comorbidities and smoking status, where appropriate.

HRs of similar magnitude associated with maximum lifetime BMI. We also found that low socioeconomic status as measured by education level was not significantly associated with poor survival in our cohort. Although unlikely to be misclassified, it may be possible that education is a poor measure of socioeconomic status in the Australian population, so we additionally examined household income as a proxy measure of socioeconomic status and again we found no association. Household income is not without limitations, however, as 14% of patients declined to report their income, and this measure may be a misleading indicator of socioeconomic status among the retired and students. Thus, although we cannot completely rule out misclassification as an explanation for the lack of association with socioeconomic status in our data, we consider the likelihood to be low.

The strengths and limitations of our study should be considered in interpreting these results. Our study has a number of strengths, including the large population-based prospective design combining data from the original case–control study with subsequent retrieval of clinical characteristics from medical records and complete follow-up on outcomes through the NDI. However, there were a number of eligible patients who did not participate in the original case–control study due to illness or death ($n = 258$), so our study sample was almost certainly "healthier" than the general population of patients with ESCC, because they survived long enough to participate in the case–control study (median time from diagnosis to consent was 118 days). Indeed, overall survival in this cohort (31% at 5 years) was higher than national figures, although we have no reason to believe that this would have affected the internal validity of the study, because we had complete follow-up on all participants.

Problems of reliability in self-reported lifestyle factors cannot be excluded, although this information was obtained before the outcome of interest (death), therefore differential recall between patients with short or long survival is unlikely. For alcohol, we minimized the possibility of differential recall bias due to early disease symptoms by eliciting comprehensive measures of lifetime exposure to ensure that premorbid changes in drinking patterns were recorded and integrated into measures of overall intake. There may be some random misclassification, but it is more likely that patients would have underestimated their alcohol consumption rather than the other way, thus the observed result may even underestimate the true effect.

A limitation of our study was the number of patients for whom an accurate AJCC stage was unable to be determined (52%). This was unfortunate but not surprising given that patients for our study were ascertained from across the population, including major treatment centers, provincial hospitals and outpatient clinics. Not all patients received the same level of investigations prior to treatment. Regardless, the lack of accurate staging data for some patients does not invalidate these findings because for the analyses presented here, tumor stage was simply a potential confounder of the associations between the exposures of interest (alcohol, tobacco and other premorbid factors) and the primary outcome (all cause mortality). Although we were unable to accurately determine AJCC stage for some patients, we did have complete treatment and follow-up information on all patients, and our data show that survival

for patients in the "undetermined" group was similar to those with AJCC stage 2 disease. Moreover, to control for potential confounding by AJCC stage, we included all patients in the main models and retained those with undetermined status as a separate category. Regardless, our sensitivity analyses suggested that AJCC stage had little impact on the associations between alcohol and survival, and that risk estimates for alcohol derived from models with and without terms for AJCC were very similar. The impact of competing risks is another potential source of bias; however, in our study esophageal cancer was the cause of death for 91% of patients for whom we had ICD coded cause of death information. Moreover, we adjusted for presence of comorbidities, which may influence survival in our analyses. Thus, we believe it unlikely that the effect of alcohol on survival is due to excessive mortality of alcohol drinkers due to causes other than esophageal cancer. It is also possible that patients may have changed their lifestyle patterns after diagnosis; however, we were interested in the effect of premorbid factors on survival. Although our case group had a relatively high proportion of females (43%), the sex distribution was similar to the distribution of all potentially eligible ESCC cases notified to the Australian National Cancer Statistics Clearing House (2002), so we consider bias with respect to the sex distribution of cases to be unlikely. Finally, because of the small number of non-white patients in our study, and exclusion of people over the age of 79 years, our findings are limited to younger, white populations.

Confounding remains a potential explanation for our findings because patients who consume alcohol may delay diagnosis and treatment, resulting in poorer survival. In our data, we found no evidence that heavy drinkers with general medical symptoms unrelated to ESCC were any more or less likely to see a doctor compared to nondrinkers or light drinkers. However, patients who regularly consumed alcohol were more likely to have AJCC stage III-IV disease and less likely to have had an esophageal resection attempted, compared to patients who consumed alcohol infrequently. Although we carefully adjusted for each of these factors, it is difficult (if not impossible) to fully control their effects in a retrospective study. In stratified analyses, the poorer survival associated with alcohol consumption appeared to be greater among older patients, those with late AJCC stage and nonsurgical patients, although tests for statistical interactions were uniformly nonsignificant. Whether these differences reflect chance or effect modification requires further investigation; however, it is unlikely that these fully explain the poorer prognosis associated with alcohol consumption.

Assuming the association reported here is not the result of error, then the question arises as to whether worse survival among patients who regularly consumed alcohol is causal. Several biological mechanisms may explain the effect of alcohol on survival as it may alter the behavior of a tumor directly. For example, alcohol may induce ESCC tumors to develop a more aggressive phenotype facilitating metastatic spread and, when coupled with genetic susceptibilities with acetaldehyde elimination modulated by *ADH1B* and *ALDH2* genotypes, result in appreciably younger age at diagnosis of ESCC.[27] It is also possible that alcohol might influence survival indirectly through systemic effects, such as compromising the immune system and contributing to impaired host defence against cancerous cells.[28]

In summary, we have assessed the effect of prediagnostic demographic and lifestyle factors on survival among patients with ESCC in one of the largest studies to date, with adjustment for key treatment and clinicopathological predictors and complete follow-up through the national death index. Our findings suggest worse survival from ESCC can be added to the list of harms attributed to heavy alcohol consumption. Further data are required to confirm these findings and to increase the precision of effect sizes for these exposures.

Acknowledgements

The authors acknowledge assistance from Dr. Shahram Sadeghi and Dr. Harish Babu for pathology abstractions and Dr. Nirmala Pandeya for data cleaning and programming.

References

1. Jemal A, Siegel R, Xu JQ, Ward E. Cancer Statistics, 2010. *CA Cancer J Clin* 2010;60: 277–300.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010;127:2893–917.
3. Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003;349:2241–52.
4. Cook MB, Chow WH, Devesa SS. Oesophageal cancer incidence in the United States by race, sex, and histologic type, 1977-2005. *Br J Cancer* 2009;101:855–9.
5. Curado MP, Edwards B, Shin HR, Storm H, Ferlay J, Heanue M, Boyle P, eds. Cancer incidence in five continents, vol. IX. IARC Scientific Publications No. 160. Lyon: IARC, 2007.
6. Pandeya N, Williams G, Green AC, Webb PM, Whiteman DC. Alcohol consumption and the risks of adenocarcinoma and squamous cell carcinoma of the esophagus. *Gastroenterology* 2009;136:1215–24.
7. Pandeya N, Williams GM, Sadhegi S, Green AC, Webb PM, Whiteman DC. Associations of duration, intensity, and quantity of smoking with adenocarcinoma and squamous cell carcinoma of the esophagus. *Am J Epidemiol* 2008;168:105–14.
8. Freedman ND, Abnet CC, Leitzmann MF, Mouw T, Subar AF, Hollenbeck AR, Schatzkin A. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *Am J Epidemiol* 2007;165:1424–33.
9. Vaughan TL, Davis S, Kristal A, Thomas DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 1995;4:85–92.
10. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington, DC: AICR, 2007.
11. US Department of Health and Human Services, Department of Agriculture. Dietary guidelines for Americans, 6th edn. Washington, DC: US Government Printing Office, 2005.
12. Steevens J, Schouten LJ, Goldbohm RA, van den Brandt PA. Alcohol consumption, cigarette smoking and risk of subtypes of oesophageal and gastric cancer: a prospective cohort study. *Gut* 2010;59:39–48.
13. Brown LM, Hoover R, Silverman D, Baris D, Hayes R, Swanson GM, Schoenberg J, Greenberg R, Liff J, Schwartz A, Dosemeci M, Pottern L, et al. Excess incidence of squamous cell esophageal cancer among US black men: role of social class and other risk factors. *Am J Epidemiol* 2001;153:114–22.
14. Steffen A, Schulze MB, Pischon T, Dietrich T, Molina E, Chirlaque MD, Barricarte A, Amiano

P, Quiros JR, Tumino R, Mattiello A, Palli D, et al. Anthropometry and esophageal cancer risk in the European Prospective Investigation into Cancer and Nutrition. *Cancer Epidemiol Biomarkers Prev* 2009;18:2079–89.
15. Freedman ND, Park Y, Subar AF, Hollenbeck AR, Leitzmann MF, Schatzkin A, Abnet CC. Fruit and vegetable intake and esophageal cancer in a large prospective cohort study. *Int J Cancer* 2007;121:2753–60.
16. Sadeghi S, Bain CJ, Pandeya N, Webb PM, Green AC, Whiteman DC. Aspirin, nonsteroidal anti-inflammatory drugs, and the risks of cancers of the esophagus. *Cancer Epidemiol Biomarkers Prev* 2008;17:1169–78.
17. Trivers KF, De Roos AJ, Gammon MD, Vaughan TL, Risch HA, Olshan AF, Schoenberg JB, Mayne ST, Dubrow R, Stanford JL, Abrahamson P, Rotterdam H, et al. Demographic and lifestyle predictors of survival in patients with esophageal or gastric cancers. *Clin Gastroenterol Hepatol* 2005;3:225–30.
18. Sundelof M, Lagergren J, Ye WM. Patient demographics and lifestyle factors influencing long-term survival of oesophageal cancer and gastric cardia cancer in a nationwide study in Sweden. *Eur J Cancer* 2008;44:1566–71.
19. Shitara K, Matsuo K, Hatooka S, Ura T, Takahari D, Yokota T, Abe T, Kawai H, Tajika M, Kodaira T, Shinoda M, Tajima K, et al. Heavy smoking history interacts with chemoradiotherapy for esophageal cancer prognosis: a retrospective study. *Cancer Sci* 2010;101:1001–6.
20. Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373–83.
21. Smithers BM, Fahey PP, Corish T, Gotley DC, Falk GL, Smith GS, Kiroff GK, Clouston AD, Watson DI, Whiteman DC. Symptoms, investigations and management of patients with cancer of the oesophagus and gastro-oesophageal junction in Australia. *Med J Aust* 2010;193:572–7.
22. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC cancer staging manual, 7th edn. New York, NY: Springer, 2010.
23. Rothman KJ, Greenland S. Modern epidemiology, 2nd edn. Philadelphia: Lippincott-Raven, 1998.
24. Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. *Eur J Epidemiol* 2005;20: 575–9.
25. Mayne ST, Cartmel B, Kirsh V, Goodwin WJ. Alcohol and tobacco use prediagnosis and postdiagnosis, and survival in a cohort of patients with early stage cancers of the oral cavity, pharynx, and larynx. *Cancer Epidemiol Biomarkers Prev* 2009;18:3368–74.
26. Deleyiannis FWB, Thomas DB, Vaughan TL, Davis S. Alcoholism: independent predictor of survival in patients with head and neck cancer. *J Natl Cancer Inst* 1996;88:542–9.
27. Lee CH, Wu DC, Wu IC, Goan YG, Lee JM, Chou SH, Chan TF, Huang HL, Hung YH, Huang MC, Lai TC, Wang TN, et al. Genetic modulation of ADH1B and ALDH2 polymorphisms with regard to alcohol and tobacco consumption for younger aged esophageal squamous cell carcinoma diagnosis. *Int J Cancer* 2009;125:1134–42.
28. Giovannucci E, Rimm EB, Ascherio A, Colditz GA, Spiegelman D, Stampfer HJ, Willett WC. Smoking and risk of total and fatal prostate cancer in United States health professionals. *Cancer Epidemiol Biomarkers Prev* 1999;8:277–82.

Journal of the American College of Cardiology
Vol. 58, No. 15, 2011

ISSN 0735-1097/$36.00
Published by Elsevier Inc.
doi:10.1016/j.jacc.2011.07.011

EDITORIAL COMMENT

When the Stomach Rules the Heart

Dyspnea as a Neglected Complication of a Large Hiatal Hernia*

Thomas H. Marwick, MBBS, PHD

Cleveland, Ohio

Hiatal hernia is a common condition; its exact prevalence is uncertain because of disagreement about its definition, but some sources suggest that it is present in more than 50% of individuals older than the age of 50 years (1). Cardiologists are most commonly involved in the care of patients with hiatal hernia because of the diagnostic challenge posed by gastroesophageal reflux in the differential diagnosis of chest pain. This entity also requires attention in relation to incidental findings on chest x-ray, difficulties in the performance of transesophageal echocardiography, and external compression of the left atrium causing an apparent left atrial mass (2,3). Although an 84% prevalence of dyspnea has been reported in a previous description of paraesophageal hernia repair on pulmonary function (4), dyspnea is not widely recognized as an important presentation of hiatal hernia. Indeed, cardiologists are all too familiar with the exercise implications of the stomach ruling the heart, and dyspnea in these circumstances is often attributed to coexistent obesity, which is a commonly associated with hiatal hernia (5).

See page 1624

The perception that this diagnosis is usually considered a finding of only limited interest to cardiologists might be challenged by a paper in this issue of the *Journal* by investigators in Sydney, Australia (6). In this study, 30 patients were studied prospectively using resting and stress echocardiography, cardiac computed tomography, and respiratory function testing before and after laparoscopic repair of large hiatal hernias. Despite the presence of normal pulmonary function, 83% of these patients had exertional dyspnea, and this problem improved after surgery. Moderate to severe left atrial compression was present in 77%, and this was associated with the degree of functional impairment. Although coronary sinus compression was noted and might be expected to be associated with coronary hyperemia, this did not seem to be linked to the degree of functional disturbance. The improvement of functional class and exercise capacity after surgery was associated with resolution of cardiac compression. Indeed, the change of left atrial diameter on echocardiography was the only independent correlate of exercise capacity improvement after surgery.

A particular focus of this paper is on the mechanistic effects of hiatal hernia on dyspnea. Potential explanations include disturbances of respiratory function, diaphragmatic motility, and disturbances of ventilation and perfusion, as well as esophageal reflux causing asthma (7). The impact of hernia surgery on dyspnea matches that reported in previous work (8,9). Although there was indeed a modest improvement of pulmonary function, these tests were normal at baseline, and it seems unlikely that this was the only explanation for the functional improvements after surgery, especially as spirometry was not disturbed to the level usually associated with functional compromise. Cardiac compression by hiatal hernia has been described in individual case reports, but the mechanism of this association has not been not well defined (10–12). The results of this study provide evidence of left atrial, pulmonary venous, and coronary sinus compression by large hiatal hernias, with improvement of left ventricular and left atrial dimensions, as well as a normalization of atrial inflow velocities after surgery (6). Indeed, the resolution of cardiac compression is a mechanism that explains improvement in functional capacity in other conditions ranging from pectus excavatum to pericardial constriction (13,14). Although other factors such as exercise training can lead to improved exercise capacity, the amount of change in exercise capacity (from 75 ± 24% to 112 ± 23% predicted) was more than could be anticipated from exercise training alone. How then is the clinician to make use of this new observation? First, although the >80% prevalence of dyspnea may be inflated by the performance of complete testing in 30 of 52 operative patients (perhaps the most symptomatic patients), it would have to be concluded that dyspnea is a common symptom among individuals with large, mainly paraesophageal hiatal hernias. These hernias can be recognized by the presence of >30% of the stomach being intrathoracic, producing a significant mass effect in the chest. As a corollary to this observation, detailed evaluation for compression is not warranted in the setting of small hiatal hernias. Second, although the standard therapeutic strategy for symptoms of esophageal reflux (which is based on pharmacotherapy and behavioral change) will not be altered, the recognition of reduced exercise capacity as a complication of hiatal hernia may have a modest effect on the consideration of surgery, which is usually performed because of the failure of medical therapy or the development of complications. Extrinsic compression should certainly be considered when syncope or dyspnea are provoked by lying down, typically after a large

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio. Dr. Marwick has reported that he has no relationships relevant to the contents of this paper to disclose.

meal. In this circumstance, distention of the hernial sac, as was performed in this example by fluid loading before testing, may be a valuable "stress test." Finally, this work, from 4 specialties (cardiology, gastroenterology, pulmonary medicine, and radiology) and using 4 modalities (echocardiography, computed tomography, exercise testing, respiratory function) should serve to remind us that the recognition of interactions between common conditions through multidisciplinary and multimodality investigation of problems across specialty "silos" will identify new insights (15).

Reprint requests and correspondence: Dr. Thomas H. Marwick, Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44195. E-mail: marwict@ccf.org.

REFERENCES

1. Mittal RK. Hiatal hernia: myth or reality? Am J Med 1997;103: 33S–9S.
2. Dencker M, Missios A. How to misuse echo contrast. Cardiovasc Ultrasound 2009;7:4.
3. Khouzam RN, Akhtar A, Minderman D, Kaiser J, D'Cruz IA. Echocardiographic aspects of hiatal hernia: a review. J Clin Ultrasound. 2007;35:196–203.
4. Low DE, Simchuk EJ. Effect of paraesophageal hernia repair on pulmonary function. Ann Thorac Surg 2002;74:333–7.
5. Friedenberg FK, Xanthopoulos M, Foster GD, Richter JE. The association between gastroesophageal reflux disease and obesity. Am J Gastroenterol. 2008;103:2111–22.
6. Naoum C, Falk GL, Ng ACC, et al. Left atrial compression and the mechanism of exercise impairment in patients with a large hiatal hernia. J Am Coll Cardiol 2011;58:1624–34.
7. Havemann BD, Henderson CA, El-Serag HB. The association between gastro-oesophageal reflux disease and asthma: a systematic review. Gut. 2007;56:1654–64.
8. Zhu JC, Becerril G, Marasovic K, Ing AJ, Falk GL. Laparoscopic repair of large hiatal hernia: impact on dyspnoea. Surg Endosc 2011 Jun 3 [E-pub ahead of print].
9. Low DE, Simchuk EJ. Effect of paraesophageal hernia repair on pulmonary function Ann Thorac Surg 2002;74:333–7.
10. Lindner U, Paetzel M, Haas CS. An unusual cause of dyspnea in a patient with prior mitral valve annuloplasty and congestive heart failure. J Thorac Cardiovasc Surg 2011;141:1313–4.
11. van der Leest K, Bogaard J, Rudolphus A, et al. Paraesophageal hiatal hernia-induced dyspnea. Respiration 2009;78:105.
12. Hunt GS, Gilchrist DM, Hirji MK. Cardiac compression and decompensation due to hiatus hernia. Can J Cardiol 1996;12:295–6.
13. Neviere R, Montaigne D, Benhamed L, et al. Cardiopulmonary response following surgical repair of pectus excavatum in adult patients. Eur J Cardiothorac Surg 2011 May 11 [E-pub ahead of print].
14. Ling LH, Oh JK, Schaff HV, et al. Constrictive pericarditis in the modern era: evolving clinical spectrum and impact on outcome after pericardiectomy. Circulation 1999;100:1380–6.
15. Tinetti ME, Studenski SA. Comparative effectiveness research and patients with multiple chronic conditions. N Engl J Med 2011;364: 2478–81.

Key Words: exercise capacity ■ hiatal hernia ■ left atrial compression.

Cancer Causes Control (2010) 21:1475–1484
DOI 10.1007/s10552-010-9576-8

ORIGINAL PAPER

Eating habits and risk of esophageal cancers: a population-based case–control study

Torukiri I. Ibiebele · Adele R. Taylor · David C. Whiteman · Jolieke C. van der Pols · for the Australian Cancer Study

Received: 3 December 2009 / Accepted: 29 April 2010 / Published online: 14 May 2010

Abstract
Objective Eating behaviors, such as the timing, speed of eating, and frequently consuming hot drinks, fried, spicy, or barbecued foods may be associated with increased risks of esophageal cancer. We analyzed data from a population-based case–control study to examine whether eating behaviors are associated with risk of esophageal cancer.
Methods Self-administered questionnaire was used to collect data on demographic, socioeconomic, and lifestyle characteristics, and a food frequency questionnaire was used to collect data on dietary behaviors from 1,472 control subjects, 286 cases with adenocarcinoma of the esophagus, 320 cases with esophagogastric junction adenocarcinoma (EGJAC), and 238 cases with esophageal squamous cell carcinoma (ESCC). We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional multivariable adjusted logistic regression, adjusting for confounders.
Results Frequency of hot drinks, home-fried foods, barbecued meats, spicy foods, and the timing of eating an evening meal were not associated with esophageal cancer risk. Those who frequently consumed fried 'take-away' food had increased risks of EGJAC (OR = 1.44, 95% CI = 1.01–2.05; p value = 0.04). Eating speed was inversely associated with ESCC risk (p for trend = 0.001).
Conclusion We found no evidence that consumption of hot drinks, barbecued meats, spicy foods, or the timing of the evening meal are associated with increased risk of esophageal cancer in this Australian population. Associations with consumption of fried 'take-away' foods and eating speed await confirmation in future studies.

Keywords Esophageal neoplasms · Case–control study · Eating habits · Fried foods · Hot beverages

T. I. Ibiebele (✉) · A. R. Taylor · D. C. Whiteman · J. C. van der Pols
Cancer and Population Studies Group, Clive Berghofer Cancer Research Centre, Queensland Institute of Medical Research, Herston, QLD 4029, Australia
e-mail: Torukiri.Ibiebele@qimr.edu.au

Introduction

Esophageal cancer is the eighth most common cancer by incidence, and the sixth most common cause of cancer-related deaths worldwide [1, 2]. There are two histological types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC) [2]. The incidence of EAC has been increasing in Western countries during the past three decades and now occurs more frequently than ESCC [3]. EAC occurs more commonly in men, and the incidence rises with age. ESCC has been strongly associated with high-level exposure to alcohol and tobacco smoking in western populations [4], while EAC has been associated with obesity, tobacco smoking, gastro-esophageal reflux disease (GERD) and Barrett's esophagus [5]. The incidence of EAC has been increasing in Australia in line with trends observed elsewhere [6, 7]. A recent publication reported that in the two decades prior to 2005, the annual percentage change in the incidence of EAC in New South Wales, Australia [8] in men and women was 4.2% (95% CI = 2.7–5.8%) and 4.3% (95% CI = 1.8–7.0%), respectively. These rapid changes in incidence prompted the present study to identify risk factors for adenocarcinomas of the esophagus.

Some epidemiological studies have reported associations between some lifestyle and dietary behaviors and esophageal cancers [9, 10] albeit with inconsistent results. For example, a recent study conducted in Iran reported that

people who drink tea at very high temperatures have markedly increased risks of ESCC, possibly due to thermal injury to the esophagus [11]. This finding has not been universal however [12]. There is also some evidence that consuming a diet rich in *fried* foods, particularly potatoes, [13] is related to moderate increase in esophageal cancer risk probably due to the formation of acrylamide, a probable human carcinogen in carbohydrate-rich foods [14]. Other studies have failed to confirm this finding [15]. Other dietary practices that have been associated with esophageal cancer include barbecuing meat [16–18], eating 'spicy' foods [19], eating evening meals late at night [20], and eating quickly with inadequate chewing of food [21].

We have used data collected in a nation-wide study of esophageal cancers to determine whether eating behaviors are associated with esophageal cancer risk in a western population such as Australia.

Materials and methods

A detailed description of the methods for this population-based case–control study has been published previously [22]. In summary, adult participants aged 18–79 with a histologically confirmed primary invasive EAC or esophagogastric junction adenocarcinoma (EGJAC) or ESCC of the esophagus diagnosed between 2001 and 2005 were identified through major treatment centers throughout Australia; those missed at these centers were identified by state-based cancer registries (notification of cancer diagnosis is mandatory in all states of Australia). Of 1,191 cases invited to participate in the study through the treatment centers, 928 (78%) agreed to take part, while of 386 cases invited to participate from the cancer registries, 253 (66%) agreed to take part. A total of 1,181 (75%) cases consented to take part in the study. Controls were randomly selected from the Australian Electoral Roll (enrollment is compulsory). We prospectively sampled controls from within strata of age (in 5-year age groups), sex, and state of residence. Female controls were intentionally over-sampled at all ages to accommodate their simultaneous enrollment in a parallel case–control study of ovarian cancer. Of 3,042 controls who were contacted and invited to take part in the study, 1,680 (55%) agreed to take part. In total 1,102 cases and 1,580 controls returned the main risk factor questionnaire. Details of the histological type and anatomical site of each tumor were abstracted from diagnostic pathology reports. Anatomical sites of tumors were categorized into 'esophageal' and 'esophagogastric junction' tumors according to the WHO classification [23]. The study was approved by the human research ethics committee of the Queensland Institute of Medical Research and all participating institutions. All study participants provided informed written consent to take part.

Dietary data collection

Dietary data were obtained using a 135-item semi-quantitative food frequency questionnaire (FFQ). Controls were asked to report how often they consumed a specified amount of food item on the FFQ in the previous year. Cases were asked to report their usual frequency of consumption in the year before their diagnosis or if their diet had changed in the last 6–12 months, their usual diet. The FFQ was based on the instrument developed by Willett and colleagues [24] but was modified for use in Australia. The FFQ was validated against 12-day weighed food records and serum biomarkers and was found to provide reproducible intake estimates [25–27]. The FFQ estimates showed good correlations with weighed food records for consumption of tea ($r = 0.88$) and coffee($r = 0.81$) [26]. Participants reported on average how many times they consumed a specified portion size of regular coffee (instant, filtered, plunger), decaffeinated coffee (instant, filtered, plunger), tea (not herbal or green teas), and green tea. The response options ranged from 'never' to '4+ times per day'. For analysis regarding the number of cups of hot beverages consumed, all types of coffee and all types of tea were combined to form the total amount of all hot drinks (tea and coffee, any type) consumed. Daily total intake of fruits and vegetables (in grams), total energy intake (in kJ) and caffeine intake (in milligrams) were calculated using food composition tables in Australia as contained in the electronic version of Nutrient Tables for use in Australia (NUTTAB) 2006 [28]. In addition to the main FFQ items, all participants completed additional questions about the usual temperature at which tea or coffee or (other hot beverages) was consumed (on a 6-point scale ranging from 'room temperature', 'luke-warm', 'warm', 'warm to hot', 'hot', to 'very hot') and the frequency of consumption of fried food (prepared at home or 'take-away'), spicy foods, and barbecued meats. For barbecued meat, participants were asked how 'well-done' was the meat they tended to eat, with responses as follows: 'I never eat BBQ meat', 'rare (still some blood)', 'medium-rare (pink in the middle)', 'medium (lightly cooked all the way through)' or 'well done'. We asked participants how often they ate foods that were 'hot and spicy' (e.g., curry, chili, Tabasco) during the past 10 years; with responses ranging from 'never', 'less than once a month', 'about once a month', 'between once a month and once a week', 'about once a week', 'several times a week', and 'everyday'. Finally, we asked participants questions relating to eating speed and timing of evening meals.

Non dietary data collection

We collected data about other factors using a self-administered questionnaire. Information was collected on demography (age, sex), social background (education, income), as well as height and weight 1 year ago (1 year before diagnosis for cases). We calculated body mass index (BMI) by dividing weight in kilograms by the square of height in meters. BMI categories used for analysis were <25 kg/m^2—'normal weight'; 25–29.9 kg/m^2—'overweight'; and ≥30—'obese'. Participants were asked whether, over their whole life, they had ever smoked more than 100 cigarettes, cigars, or pipes; positive responses elicited further questions about ages at which they started and stopped smoking and typical daily consumption. We derived the number of pack years of tobacco exposure by dividing the number of cigarettes smoked daily by 20 and multiplying by the total number of years smoked. To assess lifetime alcohol consumption we asked participants to report the frequency with which they consumed different classes of alcohol (low alcohol beer, regular beer, white wine, red wine, port/sherry, and spirits/liqueurs) between ages 20–29, 30–49, and ≥50, as applicable. Total alcohol consumption was summed across all age groups for all types of alcohol, from which we calculated a weighted average number of standard drinks (10 g ethanol) consumed per week between age 20 years and current age. We assessed the frequency of symptoms of gastro-esophageal reflux defined as the presence of heartburn ('a burning pain behind the breastbone after eating') or acid reflux ('a sour taste from acid or bile rising up into the mouth or throat') 10 years before diagnosis. We also assessed frequency of use of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin, and acid suppressants including proton pump inhibitors (PPIs) during the past 5 years.

Exclusion and final sample size

Of the 1,102 cases and 1,580 controls who returned the main risk factor questionnaire, 155 (141 cases and 14 controls) participants had no opportunity to complete a FFQ because the nutrition component of the study commenced 6 months after the main study, giving a total of 961 cases and 1,566 eligible controls. After further exclusion of participants who omitted responses to 10% or more of FFQ items, and those with implausible energy intake according to Willett's criteria [24], we had 844 cases (286 EAC, 320 EGJAC, 238 ESCC) (88% of those who completed a FFQ),and 1,472 (94%) controls left for these dietary analyses.

Statistical analysis

The distributions of demographic characteristics and potential risk factors were compared among cases and controls using chi-square test for proportions. We estimated the risk of EAC, EGJAC and ESCC associated with categories of exposure variables by calculating the odds ratios (ORs) and 95% confidence intervals (CIs) for each of the case groups using unconditional multivariable logistic regression. The multivariable logistic regression model adjusted for the confounding effects of age, sex, educational status, cumulative history of smoking in pack years, heartburn and acid reflux symptoms in previous 10 years, body mass index in previous year, aspirin use in previous 5 years, vegetable, fruit, and total energy intake. Tests for linear trend were performed by treating the categorical variables as continuous predictors in the multivariable regression model. Category values were assigned as the midpoint of the range for each category. For beverage drinking temperature variables, we combined the lowest two categories and assigned the following values for trend analysis only: 'room temperature/luke-warm' 35°C (reference), 'warm' 50°C, 'warm to hot' 60°C, hot 65°C, and very hot 70°C. To assess the association between temperature of tea and coffee and esophageal cancer, we adjusted further for caffeine intake. All analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, NC). p-values were two sided, and $p < 0.05$ was considered statistically significant.

Results

Characteristics of cases and controls are presented in Table 1. Esophageal cancer cases were more likely to be older (60+ years) and to be heavy smokers (30+ pack years) than controls. Cases with EAC and EGJAC were more likely to be men, obese, and to experience symptoms of reflux (monthly or more often) than ESCC cases and controls. ESCC cases were more likely to be heavy alcohol consumers (≥21 standard drinks/week) than EAC and EGJAC cases and controls. On average, controls were less likely (14.5%) to use PPIs than EAC (39.2%), EGJAC (37.2%), or ESCC (31.9%) cases.

Table 2 details the risk estimates for the associations between eating habits and risk of esophageal cancer. We found no evidence that those who ever drank hot tea or coffee had higher or lower risks of EGJAC or ESCC than those who did not after adjusting for confounders. Inclusion of income and PPI to the final model did not materially change the risk estimates. There was a suggestion of an elevated EAC risk among those who ever consumed hot tea or coffee but this is probably attributable to the very small number of EAC cases that never consumed hot tea or coffee. While the relative risks of esophageal cancer were not significantly different from the null with increasing temperature of consumption, the point estimates of risk for

Table 1 Distribution of selected characteristics among participants of the Australian Cancer Study

Total number[a]	Controls (n = 1,472) n (%)	EAC (n = 286)[b] n (%)	p Value	EGJAC (n = 320)[c] n (%)	p Value	ESCC (n = 238)[d] n (%)	p Value*
Age in previous year (years)							
<30–49	260 (18)	22 (8)		25 (8)		15 (7)	
50–59	382 (26)	73 (26)		90 (28)		54 (23)	
60+	830 (56)	191 (67)	<0.01	205 (64)	<0.01	161 (70)	<0.01
Gender							
Female	498 (34)	28 (10)		47 (15)		90 (39)	
Male	974 (66)	258 (90)	<0.01	273 (85)	<0.01	140 (61)	<0.12
Educational status							
High school only	602 (41)	130 (45)		118 (37)		131 (57)	
Trade certificate or apprenticeship	332 (23)	80 (28)		90 (28)		43 (19)	
Technical college or diploma	311 (21)	57 (20)		78 (24)		37 (16)	
University degree	227 (15)	19 (7)	<0.01	34 (11)	<0.012	19 (8)	<0.01
Body mass index in previous year							
<25.0 kg/m^2 (Normal weight)	527 (36)	56 (20)		84 (27)		121 (55)	
25–29.9 kg/m^2 (Overweight)	629 (43)	117 (42)		124 (40)		69 (31)	
>30.0 kg/m^2 (Obese)	300 (21)	107 (38)	<0.01	105 (36)	<0.01	30 (14)	<0.01
Cumulative history of smoking (in pack years)							
Never smoker	655 (45)	70 (24)		76 (24)		55 (24)	
0–14.9	376 (26)	59 (21)		64 (20)		45 (20)	
15–29.9	191 (13)	54 (19)		71 (22)		47 (20)	
30+	250 (17)	103 (36)	<0.01	109 (34)	<0.01	83 (36)	<0.01
Life mean alcohol consumption (standard drinks/week)[e]							
None	184 (13)	21 (7)		31 (10)		31 (13)	
<1–6 Drinks/week	522 (35)	75 (26)		91 (28)		59 (26)	
7–20 Drinks/week	477 (32)	107 (37)		108 (34)		47 (20)	
≥21/Week	289 (20)	83 (29)	<0.01	90 (28)	0.003	93 (40)	<0.01
Heartburn and acid reflux symptoms in previous 10 years							
Never	639 (43)	63 (22)		93 (29)		108 (47)	
<Monthly	450 (31)	39 (14)		49 (15)		28 (12)	
>Monthly but <weekly	211 (14)	65 (23)		72 (23)		32 (14)	
>Weekly but <daily	117 (8)	69 (24)		72 (23)		33 (14)	
Daily	55 (4)	50 (18)	<0.01	34 (11)	<0.01	29 (13)	<0.01
Aspirin use in previous 5 years							
Never	643 (44)	136 (48)		140 (44)		109 (47)	
Occasionally	570 (39)	94 (33)		118 (37)		85 (37)	
<Weekly to at least weekly	259 (18)	56 (20)	0.17	62 (20)	0.71	36 (16)	0.55
Proton pump inhibitors use in previous 5 years							
No	1,258 (85.5)	174 (60.8)	<0.01	210 (62.8)	<0.01	156 (68.1)	<0.01
Yes	214 (14.5)	112 (39.2)		119 (37.2)		73 (31.9)	

* p value estimated using chi-square statistics

[a] Observations with missing data are not included; column percentages may not sum to 100% due to rounding

[b] EAC—esophageal adenocarcinoma

[c] EGJAC—esophagogastric junction adenocarcinoma

[d] ESCC—esophageal squamous cell carcinoma

[e] One standard drink contains 10 g of ethanol

Table 2 Adjusted odds ratios (ORs), 95% confidence intervals (CIs) for risk of esophageal cancer in relation to eating behaviors among Australian Cancer Study participants

Eating behaviors	Control subjects (*n* %)[d]	EAC[a]		EGJAC[b]		ESCC[c]	
		Cases (*n* %)[d]	OR (95% CI)	Cases (*n* %)[d]	OR (95% CI)	Cases (*n* %)[d]	OR (95% CI)
Consumption of hot tea/coffee[e,f]							
Never consume	28 (1.9)	1 (0.4)	1.00 (reference)	5 (1.6)	1.00 (reference)	2 (0.9)	1.00 (reference)
Ever consume	1,444 (98.1)	285 (99.6)	7.76 (0.91–66.0)	315 (98.4)	1.19 (0.41–3.48)	228 (99.1)	1.42 (0.30–6.73)
p Value			=0.06		=0.75		=0.66
Temperature of tea/coffee[e,f]							
Room temperature to Luke-warm	46 (3.1)	15 (5.2)	1.00 (referent)	17 (5.3)	1.00 (referent)	8 (3.5)	1.00 (referent)
Warm	84 (5.7)	28 (9.8)	1.56 (0.67–3.61)	26 (8.1)	0.92 (0.42–2.03)	20 (8.7)	1.72 (0.64–4.60)
Warm to hot	538 (36.5)	111 (38.8)	0.91 (0.44–1.86)	126 (39.4)	0.70 (0.36–1.37)	92 (40)	0.99 (0.42–2.32)
Hot	626 (42.5)	113 (39.5)	0.75 (0.37–1.54)	116 (36.3)	0.53 (0.27–1.03)	73 (31.7)	0.70 (0.30–1.65)
Very hot	150 (10.2)	18 (6.3)	0.51 (0.21–1.22)	30 (9.4)	0.61 (0.29–1.31)	35 (15.2)	1.28 (0.51–3.19)
p for trend			=0.02		=0.02		=0.32
Amount of hot drinks (tea/coffee) consumed per day[e,f]							
>0 to ≤2 Cups	305 (20.7)	54 (19)	1.00 (referent)	77 (24.1)	1.00 (referent)	49 (21.3)	1.00 (referent)
>2 to ≤4 Cups	675 (45.9)	137 (48.2)	1.10 (0.75–1.61)	141 (44.1)	0.84 (0.60–1.17)	113 (49.1)	1.03 (0.69–1.54)
>4 Cups	464 (31.5)	93 (32.6)	1.17 (0.78–1.76)	97 (30.3)	0.85 (0.59–1.22)	66 (28.7)	0.89 (0.57–1.39)
p for trend			=0.46		=0.40		=0.56
Amount of hot drinks (tea/coffee, any type) consumed and temperature of tea/coffee[e,f]							
≤2 Cups per day at room temperature to hot	177 (12.0)	32 (11.2)	1.00 (referent)	40 (12.5)	1.00 (referent)	30 (13.0)	1.00 (referent)
>2 to ≤4 Cups per day at room temperature to hot	304 (20.7)	72 (25.2)	1.15 (0.69–1.93)	82 (25.6)	1.19 (0.75–1.89)	54 (23.5)	1.02 (0.60–1.75)
>4 Cups per day at room temperature to hot	187 (12.7)	50 (17.5)	1.57 (0.90–2.73)	47 (14.7)	1.17 (0.70–1.95)	36 (15.7)	1.31 (0.73–2.36)
≤2 Cups per day at hot to very hot temperature	128 (8.7)	23 (8.0)	0.88 (0.46–1.68)	37 (11.6)	1.14 (0.66–1.97)	19 (8.3)	0.84 (0.42–1.66)
>2–4 Cups per day at hot to very hot temperature	370 (25.1)	65 (22.7)	0.90 (0.54–1.51)	59 (18.4)	0.70 (0.43–1.13)	59 (25.7)	0.98 (0.58–1.67)
>4 Cups per day at hot to very hot temperature	277 (18.8)	43 (15.0)	0.78 (0.45–1.36)	50 (15.6)	0.77 (0.47–1.26)	30 (13.0)	0.60 (0.33–1.10)
p for trend			=0.06		=0.02		=0.08
Frequency of consumption of home-fried food[e]							
<Once per week	465 (32)	85 (30)	1.00 (referent)	93 (29)	1.00 (referent)	73 (32)	1.00 (referent)
1–3 Times per week	726 (49)	140 (50)	0.85 (0.61–1.20)	157 (49)	0.87 (0.64–1.18)	110 (48)	0.87 (0.61–1.25)
4–6 Times per week	211 (14)	44 (15)	0.77 (0.49–1.22)	47 (15)	0.80 (0.52–1.22)	35 (15)	1.05 (0.65–1.71)
Daily or more than daily	70 (4.8)	17 (6)	0.55 (0.28–1.07)	23 (7)	0.81 (0.45–1.46)	12 (5)	0.52 (0.25–1.11)
p for trend			=0.07		=0.28		=0.29
Frequency of consumption of 'take-away' fried foods[e]							
<1 Per week	1,240 (84)	231 (81)	1.00 (referent)	250 (78)	1.00 (referent)	196 (85)	1.00 (referent)
≥1 Per week	232 (16)	55 (19)	1.33 (0.90–1.95)	70 (22)	1.44 (1.01–2.05)	34 (15)	1.31 (0.83–2.07)
p Value			=0.15		=0.04		=0.25
Consumption of barbecued meat[e]							
Never consume	76 (5.2)	12 (4.2)	1.00 (referent)	21 (6.6)	1.00 (referent)	25 (10.9)	1.00 (referent)
Ever consume	1,396 (94.8)	274 (95.8)	1.37 (0.68–2.77)	299 (93.4)	0.69 (0.39–1.20)	205 (89.1)	0.58 (0.34–1.01)
p Value			=0.38		=0.19		=0.06
Frequency of consumption of barbecued meat[e]							
<Weekly	1,170 (79.4)	234 (81.8)	1.00 (reference)	243 (75.9)	1.00 (reference)	176 (76.5)	1.00 (reference)

Table 2 continued

Eating behaviors	Control subjects (*n* %)[d]	EAC[a]		EGJAC[b]		ESCC[c]	
		Cases (*n* %)[d]	OR (95% CI)	Cases (*n* %)[d]	OR (95% CI)	Cases (*n* %)[d]	OR (95% CI)
≥Weekly	226 (15.4)	40 (14.0)	0.74(0.48–1.12)	56 (17.5)	1.22 (0.85–1.77)	29 (12.6)	0.99 (0.62–1.59)
p Value			=0.16		=0.28		=0.96
Preferred level of doneness of barbecued meat[e]							
Rare to medium-rare	389 (26.4)	78 (27.3)	1.00 (reference)	100 (31.3)	1.00 (reference)	58 (25.2)	1.00 (reference)
Medium to well done	1,007 (68.4)	196 (68.5)	1.06 (0.76–1.48)	199 (62.1)	0.86 (0.64–1.16)	147 (63.9)	0.91 (0.62–1.32)
p Value			=0.75		=0.31		=0.61
Frequency of consumption and cooking preference of barbecued meat[e]							
<Weekly, rare to medium–rare	300 (20.4)	63 (22.0)	1.00 (reference)	75 (23.4)	1.00 (reference)	52 (22.6)	1.00 (reference)
<Weekly, medium to well done	870 (59.1)	171 (59.3)	1.00 (0.70–1.45)	168 (52.5)	0.85 (0.61–1.19)	124 (53.9)	0.75 (0.50–1.13)
≥Weekly, rare to medium–rare	93 (6.3)	15 (5.2)	0.67 (0.34–1.33)	25 (7.8)	1.12 (0.64–1.97)	7 (3.0)	0.45 (0.18–1.10)
≥Weekly, medium to well done	133 (9.0)	25 (8.9)	0.81 (0.45–1.46)	31 (9.7)	1.06 (0.63–1.77)	22 (9.6)	1.07 (0.58–1.96)
p for trend			=0.31		=0.72		=0.73
Frequency of consumption of 'spicy' food[e]							
Never	201 (14)	50 (17)	1.00 (referent)	57 (18)	1.00 (referent)	43 (19)	1.00 (referent)
<1 Per month	492 (33)	89 (31)	0.81 (0.52–1.25)	102 (32)	0.73 (0.49–1.09)	78 (34)	0.87 (0.55–1.37)
About 1 per month	256 (17)	57 (20)	1.18 (0.72–1.91)	58 (18)	0.93 (0.59–1.47)	47 (20)	1.02 (0.61–1.71)
Between 1 per month and 1 per week	186 (13)	35 (12)	1.00 (0.58–1.73)	35 (11)	0.74 (0.44–1.25)	23 (10)	0.76 (0.41–1.41)
About once a week	222 (15)	36 (13)	0.78 (0.45–1.35)	51 (16)	0.82 (0.51–1.33)	25 (11)	0.69 (0.38–1.26)
More than 1 per week	115 (8)	19 (7)	1.00 (0.51–1.97)	17 (5)	0.75 (0.39–1.45)	14 (6)	0.86 (0.41–1.78)
p for trend			=0.96		=0.63		=0.32
Speed of eating when eating with a group of people[e]							
Slow eater (last to finish eating)	318 (22)	70 (25)	1.00 (referent)	86 (27)	1.00 (referent)	85 (37)	1.00 (referent)
Neither first nor last to finish	741 (51)	151 (53)	0.94 (0.66–1.34)	145 (45)	0.77 (0.55–1.07)	111 (48)	0.73 (0.52–1.04)
Quick eater (first to finish eating)	393 (27)	64 (22)	0.73 (0.48–1.12)	89 (28)	0.90 (0.62, 1.30)	33 (14)	0.45 (0.28–0.72)
p for trend			=0.15		=0.59		=0.001
Time of eating evening meal in previous year[e]							
Early (<7.30 pm most days)	1,197 (82)	236 (83)	1.00 (referent)	262 (82)	1.00 (referent)	178 (78)	1.00 (referent)
Late to very late (≥7.30 pm and just before bed most days)	240 (17)	47 (16)	1.21 (0.81–1.79)	52 (16)	1.08 (0.75–1.56)	47 (21)	1.34 (0.89–2.03)
Never or hardly eat in the evening	15 (1)	2 (0.7)	0.65 (0.13, 3.42)	6 (2)	1.54 (0.52–4.56)	4 (2)	1.29 (0.36–4.56)
p for trend			=0.55		0.46		0.17

[a] EAC—Esophageal adenocarcinoma

[b] EGJAC—Esophagogastric junction adenocarcinoma

[c] SCC—Esophageal squamous cell carcinoma

[d] Observations with missing data on any covariate included in the models were excluded from the analyses; column percentages may not sum to 100% due to rounding

[e] Adjusted for age continuous); gender; cumulative history of smoking in pack years (0, >0–14.9 pack years, 15–29 pack years, 30+ pack years); lifetime mean alcohol intake; heartburn and acid reflux symptoms (never, <1/month, ≥1/month, ≥1/week, ≥1/day); body mass index in previous year (<25.0 kg/m^2, 25–29.9 kg/m^2, >30.0 kg/m^2); educational status (no further education after high school, Trade/Certificate/Apprenticeship, Technical/College/Diploma, University degree); aspirin use in previous 5 years (never, <1/month, 1/month to 2–3/month, 1/week to ≥2/day); total fruit and vegetable intake (continuous) and total energy intake in kilojoules (continuous)

[f] 1 cup = 250 ml; additional adjustment for caffeine intake in milligrams (continuous)

EAC and EGJAC were consistently less than one, and the linear trend analyses suggested a significant reduction in risk with increasing temperatures of beverage consumption for both of the adenocarcinoma subtypes. No such inverse trend was seen for ESCC. The number of cups of tea or coffee consumed per day was not associated with risk of esophageal cancers. When temperature at which tea or coffee was consumed was combined with the quantity consumed, there was no association between temperature and quantity of tea or coffee consumed and risks of esophageal cancers.

There was no association between the frequency of consumption of home-fried foods and risk of esophageal cancer. However, consuming 'take-away' fried foods once a week or more was associated with an increased risk of EGJAC (OR = 1.44, 95% CI: 1.01–2.05; p for trend = 0.04) compared to less than once a week. We reanalyzed the data stratifying by median age of the study population and found a positive association between fried 'take-away' foods and EGJAC in the older study participants with higher risk estimates (OR = 2.05, 95% CI = 1.12–3.76, $p = 0.02$); there was no such association in the younger age group.

In simple dichotomous analysis, we found no evidence that barbecued meat eaters had higher risks of EAC or EGJAC; however, the data suggested a decreased ESCC risk (OR = 0.58, 95% CI = 0.34–1.01; p value = 0.06) among those who ever consumed barbecued meat. Among barbecued meat consumers, neither frequency of consumption, nor preferred level of doneness of meat, nor frequency of consumption of meat and preferred level of doneness combined was associated with risk of esophageal cancers.

Frequency of consumption of 'spicy' foods, and the time at which the evening meal was eaten were not associated with risk of the esophageal cancers. Eating speed, however, was associated with ESCC risk: compared to slow eaters (last to finish eating), quick eaters (first to finish eating) had a decreased risk of ESCC (OR = 0.44; 95% CI = 0.28–0.72; p for trend = 0.001). The timing of eating an evening meal was not associated with esophageal cancer.

Discussion

In this large population-based case–control study, we found no evidence that drinking tea or coffee at very hot temperature was associated with increased risk of esophageal cancers. Results of studies from several populations including Iran [11], Taiwan [29], Turkey [30], China [31], India [19], England and Scotland [32], South America [9], Japan [33], and Greece [34] overwhelmingly show positive associations between drinking tea or coffee at very hot temperatures and ESCC, whereas studies from Sweden [12] did not find a positive association between drinking hot beverages and EAC, EGJAC, or ESCC risk. In populations where positive associations have been reported between temperature of tea or coffee and risk of esophageal cancer, the beverages are often consumed at 'scalding' temperatures, where the beverage is kept boiling. In contrast, in those populations where tea and coffee is allowed to cool before being consumed, or where cold milk is commonly added, null or inverse associations have been reported. Our results and those from other western populations suggest that the temperatures at which 'hot' beverages are generally consumed in these settings are not associated with an increase in esophageal cancer risk. In our study, the assessment of temperature at which hot beverages were normally consumed were based on self-reports only and are therefore subject to misclassification. However, we have no reason to believe that misclassification would be differential with regard to case–control status. We cannot exclude the possibility of reverse causality, however, whereby cases with esophageal cancer modified their dietary habits in the period before diagnosis (such as avoiding the use of very hot beverages, spicy foods, or other types of food that could cause irritation or pain at meal times).

In epidemiologic studies, high-temperature cooking methods including barbecuing have been associated with carcinogenic substances such as heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PCAH) [35]. There is a paucity of data on barbecued meat intake, and very limited availability of HCA and PCAH databases that include a large number of different foods analyzed for their HCA and PCAH concentrations. As a result, reported frequencies of consumption of barbecued meats and 'levels of doneness' have often been the main methodology used to estimate the consumption of these carcinogens. Thus, comparing the range of consumption of barbecued meat as well as their HCA and PCAH content across populations is difficult. Our data suggested a lower risk of ESCC for those who *ever* (OR = 0.58, 95% CI = 0.34–1.01) compared to *never* consumed barbecued meat; however, we found no evidence that the frequency of consumption of barbecued meat or preferred level of 'doneness' was associated with esophageal cancer risk. We found no significant association between intake of BBQ meat and risk of EAC (OR = 0.74 (0.48–1.12), EGJAC (OR = 1.22 (0.85–1.77) or ESCC (OR = 0.99 (0.62–1.59). Earlier hospital-based case–control studies from Uruguay [17] and Argentina [16] found a twofold increased ESCC risk. Also, a pooled analysis of data from 5 hospital-based case–control studies from Argentina, Brazil, Paraguay, and Uruguay [9] found a slightly elevated but non-significant ESCC risk (OR = 1.22 (0.85–1.76) with daily intake of BBQ meat.

Similarly, a population-based case–control study from the United States [18] found a non-significant elevated EAC risk (OR = 1.5 (0.5–4.8) with barbecuing as a cooking method. In that same US study there was no significant association for any combination of 'doneness' preference and beef intake, but high intake of gravy made with meat juices was associated with elevated EAC risk. Thus, from these studies, there is no strong overall evidence that consumption of barbecued meat is associated with increased risk of esophageal cancer risk. In our study, none of the respondents reported barbecued meat consumption on a daily basis. Almost 80% of our study population consumed barbecued meat less than weekly, and of these, more than half (46%) consumed barbecue meat less than once per month. Consumption of barbecued meat in Australia is commonly associated with social gatherings and group meals due to the seasonal nature of this activity. It is thus plausible that a reduced frequency of barbecued meat consumption and some unmeasured confounding by social factors may be associated with this null finding.

More frequent consumption of 'take-away' fried foods (but not foods fried at home) was associated with increased risk of EGJAC in our study population. This is consistent with the findings from several studies showing similar associations with fried foods [13, 36, 37] although previous studies did not indicate whether foods were fried within or outside of the home. However, another study failed to find an association between intake of fried potatoes and esophageal cancer risk [15]. Because our study population included participants as young as 18 years, we reanalyzed our data stratified by median age of the study population (<62 years, and ≥62 years). We found no evidence of an association between the dietary characteristics studied and the two histological types of esophageal cancer in the younger age group, while in the older participants, we found higher risk estimates for the association between fried 'take-away' foods and EGJAC in the older participants (OR = 2.05, 95% CI = 1.12–3.75; p value = 0.02). Interaction between frequency of consumption of fried 'take-away' foods and age in relation to EGJAC was significant (p for interaction = 0.01). Acrylamide, a toxic substance, produced during processing (baking, broiling, frying roasting) of foods as a result of heat induced reactions between amino group of free amino acids and the carbonyl group of reducing sugars has been implicated as a causative agent [38]. Foods rich in both of these precursors are largely derived from plant sources such as potatoes and cereals (barley, rice, and wheat) but not animal foods such as poultry beef and fish [38]. A recent study that investigated the association between 'take-away' food consumption and diet quality in Australia found that consumption of 'take-away' foods was associated with poorer diet quality and higher prevalence of obesity in men than women [39]. Thus, our findings may reflect residual confounding by other risk factors for esophageal adenocarcinoma including obesity and esophageal reflux symptoms, despite our attempts to control for such effects in the analysis. In our study we found a strong association between BMI and intake of fried 'take-away' foods among cases (p value = 0.007), and a weak association between esophageal reflux and intake of fried 'take-away' food (p value = 0.08). Among cases with reflux, those who were obese (42%) were more likely to eat fried 'take-away' food once a week or more than those with normal BMI (21%) (p value = 0.04). Among cases without reflux, no significant associations were found between intake of fried 'take-away' food and BMI (p value = 0.29).

We found no association between consumption of spicy foods and esophageal cancer risk. Reports from previous studies have been mixed. Similar to our finding, a case–control study from Taiwan found no significant association between spicy condiments and esophageal cancer risk [29], while a hospital-based case–control study from India [19], and a population-based case–control study from China limited only to men [40] reported positive associations. Excessive use of chilies and other hot spices is not common in Australia, and level of use of spicy foods may not be as high as would be found in China or India where positive associations have been reported. Ethnically, our study population was very homogeneous (96% of participants identified themselves as 'White') and thus the distribution of exposures such as consumption of spicy foods or temperature at which hot beverages are consumed would be expected to be narrower than regions with greater ethnic diversity. This may have limited our ability to identify true associations.

Our data suggested that 'fast eaters' have a 55% decreased risk of ESCC compared to 'slow eaters'. This is in contrast to significant positive findings of a population-based case–control study of the association between fast eating and esophageal cancer risk in low (OR = 3.1) and high (OR = 4.0) esophageal cancer risk areas in China [21]. However, since neither study objectively measured the actual time taken to consume the meals, there is a possibility that the meaning of the term 'fast' eating within the context of each population can be interpreted differently. Also, we cannot verify whether possible early symptoms of esophageal cancer may have altered eating speed before cancer diagnosis, causing an apparent protective association of fast eating.

While we found no association between time of eating evening meal and risk of esophageal cancer, a prospective, randomized unblinded crossover trial of patients with symptomatic GERD and esophageal cancer from the United States reported a significant association between standardized late evening meal and increased supine reflux

compared to when the same meal was consumed earlier in the day [20]. It is difficult to compare our result to this finding because the 'standardized' evening meal in that study comprised a 'fast food' or 'take-away' hamburger, French fries and soft drink, while for our study, the composition of an evening meal, which was not specified, would more likely be interpreted in the Australian context as a home cooked meal.

Our study has strengths and limitations. Strengths of the study include the population-based design, the large sample size, and the rapid recruitment of cases soon after diagnosis from across the country. Weaknesses include the retrospective and self-report nature of dietary data collection. Of particular concern is that early symptoms of esophageal cancer may have caused changes in eating behavior before diagnosis among the cases. However, we repeated our analyses in the subgroup that did not report a change in their diet and observed no material differences in results. Assessment of temperature at which tea or coffee are normally consumed was based on self-report only and could not be independently verified. We were unable to quantify the amounts of heterocyclic amines or other possible causal factors in the barbecued meats to enable a more accurate determination of the association between barbecued meats and esophageal cancers.

In conclusion, we examined several behavioral factors in relation to the two histological types of esophageal cancer in our population and found null results even after stratification by age. The only significant finding was a modest increase (OR = 1.44) in EGJAC risk in relation to the consumption of fried 'take-away' foods in analysis involving all participants and a larger increase (OR = 2.05) in analysis involving older participants. Owing to the fact that this is the only significant finding out of several null results, we contend that type 1 error is the most likely explanation for this finding. Thus, our results suggest that eating habits per se are unlikely to explain the recent changes in incidence of esophageal cancer in the Australian population. We found no evidence that consumption of hot drinks, barbecued meats, spicy foods or the timing of the evening meal are associated with increased risk of esophageal cancer in this Australian population. Associations with consumption of fried 'take-away' foods and eating speed await confirmation in future studies.

Acknowledgments We are grateful to the Matt Filson Research Fund for the additional funding provided to support this project. The Australian Cancer Study was supported by the National Health and Medical Research Council (NHMRC) of Australia (Program no.199600). DCW is supported by a Principal Research Fellowship from the NHMRC of Australia.

Conflict of interest statement None of the authors had a personal or financial conflict of interest.

Appendix: The Australian Cancer Study Investigators

Investigators: David C. Whiteman MBBS, PhD, Penelope M. Webb MA, D Phil, Adele C. Green MBBS, PhD, Nicholas K. Hayward PhD, Peter G. Parsons PhD, David M. Purdie PhD.

Clinical collaborators: B. Mark Smithers FRACS, David Gotley FRACS PhD, Andrew Clouston FRACP PhD, Ian Brown FRACP.

Project Manager: Suzanne Moore RN, MPH.

Database: Karen Harrap BIT, Troy Sadkowski BIT.

Research Nurses: Suzanne O'Brien RN MPH, Ellen Minehan RN, Deborah Roffe RN, Sue O'Keefe RN, Suzanne Lipshut RN, Gabby Connor RN, Hayley Berry RN, Frances Walker RN, Teresa Barnes RN, Janine Thomas RN, Linda Terry RN MPH, Michael Connard B Sc, Leanne Bowes B Sc, MaryRose Malt RN, Jo White RN.

Clinical contributors

Australian Capital Territory: Charles Mosse FRACS, Noel Tait FRACS.

New South Wales: Chris Bambach FRACS, Andrew Biankan FRACS, Roy Brancatisano FRACS, Max Coleman FRACS, Michael Cox FRACS, Stephen Deane FRACS, Gregory L. Falk FRACS, James Gallagher FRACS, Mike Hollands FRACS, Tom Hugh FRACS, David Hunt FRACS, John Jorgensen FRACS, Christopher Martin FRACS, Mark Richardson FRACS, Garrett Smith FRACS, Ross Smith FRACS, David Storey FRACS.

Queensland: John Avramovic FRACS, John Croese FRACP, Justin D'Arcy FRACS, Stephen Fairley FRACP, John Hansen FRACS, John Masson FRACP, Les Nathanson FRACS, Barry O'Loughlin FRACS, Leigh Rutherford FRACS, Richard Turner FRACS, Morgan Windsor FRACS.

South Australia: Justin Bessell FRACS, Peter Devitt FRACS, Glyn Jamieson FRACS, David Watson FRACS.

Victoria: Stephen Blamey FRACS, Alex Boussioutas FRACP, Richard Cade FRACS, Gary Crosthwaite FRACS, Ian Faragher FRACS, John Gribbin FRACS, Geoff Hebbard FRACP, George Kiroff FRACS, Bruce Mann FRACS, Bob Millar FRACS, Paul O'Brien FRACS, Robert Thomas FRACS, Simon Wood FRACS.

Western Australia: Steve Archer FRACS, Kingsley Faulkner FRACS, Jeff Hamdorf FRACS.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55(2):74–108
2. World Cancer Research Fund/American Institute for Cancer Research (2007) Food, nutrition, physical activity, and the prevention of cancer: a global perspective. AICR, 2007, Washington

3. Gallus S, La Vecchia C (2007) Is there a link between diet and esophageal cancer? Nat Clin Pract Gastroenterol Hepatol 4:2–3
4. Holmes RS, Vaughan TL (2007) Epidemiology and pathogenesis of esophageal cancer. Semin Radiat Oncol 17:2–9
5. Chen X, Yang CS (2001) Esophageal adenocarcinoma: a review and perspectives on the mechanism of carcinogenesis and chemoprevention. Carcinogenesis 22(8):1119–1129
6. Lord RV, Law MG, Ward RL, Giles GG, Thomas RJ, Thursfield V (1998) Rising incidence of oesophageal adenocarcinoma in men in Australia. J Gastroenterol Hepatol 13(4):356–362
7. Thomas RJS, Lade S, Giles GG, Thursfield V (1996) Incidence trends in oesophageal and proximal gastric carcinoma in Victoria. Aust NZ J Surg 66(5):271–275
8. Stavrou EP, McElroy HJ, Baker DF, Smith G, Bishop JF (2009) Adenocarcinoma of the oesophagus: incidence and survival rates in New South Wales, 1972–2005. Med J Aust 191(6):310–314
9. Castellsague X, Munoz N, De Stefani E, Victora CG, Castelletto R, Rolon PA (2000) Influence of mate drinking, hot beverages and diet on esophageal cancer risk in South America. Int J Cancer 88(4):658–664
10. Mason JB, Dickstein A, Jacques PF, Haggarty P, Selhub J, Dallal G et al (2007) A temporal association between folic acid fortification and an increase in colorectal cancer rates may be illuminating important biological principles: a hypothesis. Cancer Epidemiol Biomarkers Prev 16(7):1325–1329
11. Islami F, Pourshams A, Nasrollahzadeh D, Kamangar F, Fahimi S, Shakeri R et al (2009) Tea drinking habits and oesophageal cancer in a high risk area in northern Iran: population based case–control study. BMJ 338:b929
12. Terry P, Lagergren J, Wolk A, Nyren O (2001) Drinking hot beverages is not associated with risk of oesophageal cancers in a Western population. Br J Cancer 84(1):120–121
13. Galeone C, Pelucchi C, Talamini R, Levi F, Bosetti C, Negri E et al (2005) Role of fried foods and oral/pharyngeal and oesophageal cancers. Br J Cancer 92(11):2065–2069
14. Abnett CC (2007) Carcinogenic food contaminants. Cancer Invest 25:189–196
15. Pelucchi C, Franceschi S, Levi F, Trichopoulos D, Bosetti C, Negri E et al (2003) Fried potatoes and human cancer. Int J Cancer 105(4):558–560
16. Castelleto R, Castellsague X, Munoz N, Iscovich J, Chopita N, Jmelnitsky A (1994) Alcohol, tobacco, diet, mate drinking, and esophageal cancer in Argentina. Cancer Epidemiol Biomarkers Prev 3:557–564
17. De Stefani E, Munoz N, Esteve J, Vasallo A, Victora CG, Teuchmann S (1990) Mate drinking, alcohol, tobacco, diet, and esophageal cancer in Uruguay. Cancer Res 50(2):426–431
18. Ward MH, Sinha R, Heineman EF, Rothman N, Markin R, Weisenburger DD et al (1997) Risk of adenocarcinoma of the stomach and esophagus with meat cooking method and doneness preference. Int J Cancer 71(1):14–19
19. Phukan RK, Chetia CK, Ali MS, Mahanta J (2001) Role of dietary habits in the development of esophageal cancer in Assam, the north-eastern region of India. Nutr Cancer 39(2):204–209
20. Piesman M, Hwang I, Maydonovitch C, Wong RK (2007) Nocturnal reflux episodes following the administration of a standardized meal. Does timing matter? Am J Gastroenterol 102(10):2128–2134
21. Wu M, Zhao JK, Hu XS, Wang PH, Qin Y, Lu YC et al (2006) Association of smoking, alcohol drinking and dietary factors with esophageal cancer in high- and low-risk areas of Jiangsu Province, China. World J Gastroenterol 12(11):1686–1693
22. Whiteman DC, Sadeghi S, Pandeya N, Smithers BM, Gotley DC, Bain CJ et al (2008) Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. Gut 57:173–180
23. Spechler SJ, Dixon MF, Genta R, Hainaut P, Lambert R, Siewert R (2000) Adenocarcinoma of the oesophago-gastric junction. In: Hamilton SR, Aaltonen LA (eds) Pathology and genetics Tumours of the digestive system WHO classification of tumours, vol 2, 3rd edn. IARC Press, Lyon
24. Willett W, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J et al (1985) Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 122:51–65
25. Ashton BA, Marks GC, Battistutta D, Green AC, The Nambour Study Group (1996) Under reporting of energy intake in two methods of dietary assessment in the Nambour trial. Aust J Nutr Diet 53:53–60
26. Marks GC, Hughes MC, van der Pols JC (2006) Relative validity of food intake estimates using a food frequency questionnaire is associated with sex, age, and other personal characteristics. J Nutr 136:459–465
27. McNaughton SA, Marks GC, Gaffney P, Williams G, Green AC (2005) Validation of a food-frequency questionnaire assessment of carotenoid and vitamin E intake using weighed food records and plasma biomarkers: the method of triads model. Eur J Clin Nutr 59:211–218
28. Food Standards Australia New Zealand (2007) NUTTAB 2006—Australian food composition tables. FSANZ, Canberra
29. Hung HC, Huang MC, Lee JM, Wu DC, Hsu HK, Wu MT (2004) Association between diet and esophageal cancer in Taiwan. J Gastroenterol Hepatol 19(6):632–637
30. Onuk MD, Oztopuz A, Memik F (2002) Risk factors for esophageal cancer in eastern Anatolia. Hepatogastroenterology 49:1290–1292
31. Ke L, Yu P, Zhang ZX, Huang SS, Huang G, Ma XH (2002) Congou tea drinking and oesophageal cancer in South China. Br J Cancer 86:346–347
32. Sharp L, Chilvers CE, Cheng KK, McKinney PA, Logan RF, Cook-Mozaffari P et al (2001) Risk factors for squamous cell carcinoma of the oesophagus in women: a case–control study. Br J Cancer 85:1667–1670
33. Kinjo Y, Cui Y, Akiba S, Watanabe S, Yamaguchi N, Sobue T et al (1998) Mortality risks of oesophageal cancer associated with hot tea, alcohol, tobacco and diet in Japan. J Epidemiol 8(4): 235–243
34. Garidou A, Tzonou A, Lipworth L, Signorello LB, Kalapothaki V, Trichopoulos D (1996) Life-style factors and medical conditions in relation to esophageal cancer by histologic type in a low-risk population. Int J Cancer 68(3):295–299
35. Terry PD, Lagergren J, Wolk A, Steineck G, Nyren O (2003) Dietary intake of heterocyclic amines and cancers of the esophagus and gastric cardia. Cancer Epidemiol Biomarkers Prev 12(9):940–944
36. Takezaki T, Gao CM, Wu JZ, Ding JH, Liu YT, Zhang Y et al (2001) Dietary protective and risk factors for esophageal and stomach cancers in a low-epidemic area for stomach cancer in Jiangsu Province, China: comparison with those in a high-epidemic area. Jpn J Cancer Res 92:1157–1165
37. Gao YT, McLaughlin JK, Gridley G, Blot WJ, Ji BT, Dai Q et al (1994) Risk factors for esophageal cancer in Shanghai, China. II. Role of diet and nutrients. Int J Cancer 58(2):197–202
38. Friedman M, Levin CE (2008) Review of methods for the reduction of dietary content and toxicity of acrylamide. J Agric Food Chem 56(15):6113–6140
39. Smith KJ, McNaughton SA, Gall SL, Blizzard L, Dwyer T, Venn AJ (2009) Takeaway food consumption and its associations with diet quality and abdominal obesity: a cross-sectional study of young adults. Int J Behav Nutr Phys Act 6:29
40. Wang JM, Xu B, Rao JY, Shen HB, Xue HC, Jiang QW (2007) Diet habits, alcohol drinking, tobacco smoking, green tea drinking, and the risk of esophageal squamous cell carcinoma in the Chinese population. Eur J Gastroenterol Hepatol 19(2):171–176

Gastro-oesophageal reflux symptoms and the risks of oesophageal cancer: are the effects modified by smoking, NSAIDs or acid suppressants?

N Pandeya,[1,2] P M Webb,[1] S Sadeghi,[1] A C Green,[1] D C Whiteman,[1] for the Australian Cancer Study

[1] Queensland Institute of Medical Research, Brisbane, Australia; [2] School of Population Health, The University of Queensland, Brisbane, Australia

Correspondence to: Dr D Whiteman, Division of Population Studies and Human Genetics, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Queensland 4029, Australia; david.whiteman@qimr.edu.au

Revised 20 July 2009
Accepted 20 August 2009
Published Online First 29 October 2009

ABSTRACT

Objective: To measure the extent to which risks of oesophageal cancers associated with gastro-oesophageal reflux (GOR) are modified by common factors including smoking, non-steroidal anti-inflammatory drugs (NSAIDs) and acid suppressant medications.

Design and setting: Population-based case–control study.

Participants: Cases were patients with oesophageal (OAC; n = 365) or gastro-oesophageal junction (GOJAC; n = 426) adenocarcinomas, or squamous cell carcinomas (OSCC; n = 303). Controls were sampled from a population register (n = 1580).

Main outcome measure: Odds ratio and 95% confidence interval.

Results: Frequent (at least weekly) symptoms of GOR were associated with significant 6.4-fold, 4.6-fold and 2.2-fold increased risks of OAC, GOJAC and OSCC, respectively. Under models examining effects of combined exposure, patients with frequent GOR symptoms who were also heavy smokers had markedly higher OAC risks (OR = 12.3, 95% CI 6.3 to 24.0) than those with frequent GOR who did not smoke (OR = 6.8, 95% CI 3.6 to 12.9). Similar patterns were observed for GOJAC and OSCC. Among people with frequent GOR symptoms, regular use of aspirin/NSAIDs was associated with almost two-thirds lower OAC risks (OR = 4.8, 95% CI 2.5 to 9.2) than non-users (13.9, 95% CI 6.5 to 30.0). In contrast, among those with frequent GOR symptoms, users of acid suppressants had similar OAC risks (OR 7.8, 95% CI 5.2 to 11.8) to non-users (OR 5.3, 95% CI 3.2 to 9.0).

Conclusions: People experiencing frequent GOR symptoms have markedly increased risks of OAC and GOJAC, and this effect may be greater amongst smokers. Use of aspirin and NSAIDs, but not acid suppressants, significantly reduced the risks of oesophageal cancers associated with GOR.

The incidence of adenocarcinomas of the oesophagus (OAC) and the gastro-oesophageal junction (GOJAC) has been rising rapidly in Western populations to the extent that adenocarcinomas are now more common than oesophageal squamous cell carcinoma (OSCC) in many nations.[1–3] Change over time in the prevalence of exposure to environmental factors is the most likely explanation for the observed trends. Epidemiological studies consistently identify people with frequent symptoms of gastro-oesophageal reflux (GOR) as having the highest risks of OAC, with most studies reporting significant dose–response effects.[4–6] Recently, we noted a synergistic interaction between GOR and obesity which led to markedly increased risks of OAC among people having both conditions[4 7] and it is possible that such effects have contributed to the rising incidence of OAC.[8 9]

Other factors have been identified which appear to strongly determine the risk of oesophageal cancer, and it is possible that such factors may modify the risks associated with of GOR.[10] Smoking is a risk factor for all oesophageal cancers,[11–13] and while an interaction between GOR and smoking has been observed for Barrett's oesophagus (a precursor condition for OAC),[14] this has not been explored for OAC. People who regularly consume aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) have been observed to have significantly lower risks of OAC, GOJAC and OSCC than people who do not take these medications.[15–17] Inhibition of COX-2 and related inflammatory pathways has been suggested as the mechanism to explain this apparently protective effect of aspirin and NSAIDs; if so, then this effect should be particularly apparent among people with inflammation of the lower oesophagus as characterised by frequent GOR. Patients with frequent GOR symptoms are also commonly treated with medications to suppress the production of gastric acid, including H_2 receptor blockers and proton pump inhibitors (PPIs). If repeated exposure of oesophageal epithelium to gastric acid is the underlying cause of OAC, then it might be predicted that among patients with frequent GOR, those taking acid suppressant medications would have lower risks of OAC than those not taking such medications. To date, there are scant data with which to draw conclusions on these issues.

Here, we report the findings of an investigation into the association between GOR symptoms and oesophageal cancer, and which specifically sought to identify factors that modify the association.

PATIENTS AND METHODS

Study design and participants

We analysed data from a nationwide case–control study of oesophageal cancer conducted in Australia which was approved by the research ethics committees of the Queensland Institute of Medical Research (QIMR) and participating hospitals. Details of recruitment were published in an earlier report.[4] In summary, eligible case patients were people aged 18–79 years with a histologically confirmed primary invasive cancer of the oesophagus or gastro-oesophageal junction diagnosed

between 1 July 2002 (1 July 2001 in Queensland) and 30 June 2005 in the mainland states of Australia. Patients were recruited either through major treatment centres or state-based cancer registries. A total of 1577 patients with oesophageal cancer received an invitation to participate in the study, of whom 1102 patients returned a completed questionnaire (70% of all invited; 35% of all living and deceased persons in mainland Australia who had been diagnosed with incident oesophageal cancer). For these analyses, the final numbers of case participants were 365 OAC, 426 GOJAC and 303 OSCC patients. Controls were randomly selected from the Australian Electoral Roll (enrolment is compulsory) and matched to the cases within strata of age (in 5 year age groups) and state of residence. Of 3258 potentially eligible control participants who were contacted and invited to participate, 175 were excluded (16 died, 61 too ill to participate, 98 unable to read or write in English), and 41 were lost to follow-up after initial contact. Of 3042 remaining controls, 1680 (55%) accepted the invitation and 1580 (51% of all potentially eligible controls contacted) returned completed questionnaires. Complete data for all variables included in the statistical models were available for 1545 controls, 344 OAC, 405 GOJAC and 277 OSCC.

Data collection: demographic information and health survey

Participants self-completed a health and lifestyle questionnaire, which asked about their education, occupation, general health, height and weight at the reference age (1 year ago for controls and 1 year before diagnosis for cases), smoking history, alcohol, use of aspirin and NSAIDs. We elicited a history of GOR symptoms by asking about experience of heartburn (“a burning pain behind the breastbone after eating”) or acid reflux (“a sour taste from acid or bile rising up into the mouth or throat”). Positive responses were followed by questions asking the age of first experiencing symptoms and the frequency of symptoms at ages 10–19 years, 20–29 years, 30–49 years and 50–79 years in five categories. Participants were also asked if they had ever used, separately, aspirin, other NSAIDs or paracetamol during the past 5 years, and if so, the frequency of use on a seven-point scale ranging from less than once a month up to two or more times/per day. Checklists of generic and trade names of medications licensed for use in Australia were provided to aid recall. Although aspirin and NSAIDs use were asked separately, our prior analyses have shown similar effects of the two, hence they were combined for these analyses.[18] We also asked participants to indicate whether they had ever consumed any of eight classes of medications (generic name and all brand names licensed for use in Australia at the time) used to treat heartburn, acid reflux or dyspepsia. For these analyses, we focused on participant responses to the two classes of acid suppressant medications (specifically, H_2 receptor blockers and proton pump inhibitors (PPIs)). We combined the responses into a single binary variable (“ever/never use of acid suppressant medication”) after preliminary analyses demonstrated no differences in the magnitude of effect.

Table 1 Distributions of demographic characteristics and GOR symptoms among controls and cases of OAC, GOJAC and OSCC

	Controls (n = 1545)	OAC (n = 344)	GOJAC (n = 405)	OSCC (n = 277)
Variables	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Age				
Mean (SE)	60.5 (0.3)	63.5 (0.5)	63.2 (0.5)	64.7 (0.6)
Gender				
Male	1015 (65.7)	314 (91.3)	350 (86.4)	159 (57.4)
Further studies (post-secondary)				
None	630 (40.8)	159 (46.2)	164 (40.5)	158 (57.0)
Technical college/diploma	341 (22.1)	70 (20.3)	102 (25.2)	49 (17.7)
Trade cert./apprenticeship	334 (21.6)	93 (27.0)	95 (23.5)	45 (16.2)
University	240 (15.5)	22 (6.4)	44 (10.9)	25 (9.0)
Average alcohol consumption*				
Never drinkers	171 (11.1)	25 (7.3)	32 (7.9)	36 (13.0)
<1 drink/week	101 (6.5)	11 (3.2)	15 (3.7)	17 (6.1)
1–6.99 drinks/week	485 (31.4)	82 (23.8)	108 (26.7)	58 (20.9)
7–20.99 drinks/week	495 (32.0)	123 (35.8)	142 (35.1)	58 (20.9)
21 or more drinks/week	293 (19.0)	103 (29.9)	108 (26.7)	108 (39.0)
BMI last year (kg/m^2)				
<25	563 (36.4)	69 (20.1)	104 (25.7)	158 (57.0)
25–29	663 (42.9)	146 (42.4)	167 (41.2)	80 (28.9)
⩾30	319 (20.6)	129 (37.5)	134 (33.1)	39 (14.1)
Total pack-years smoked				
Never smoker	702 (45.4)	88 (25.6)	90 (22.2)	72 (26.0)
<30	582 (37.7)	137 (39.8)	173 (42.7)	105 (37.9)
⩾30	261 (16.9)	119 (34.6)	142 (35.1)	100 (36.1)
Frequency of aspirin/NSAIDs use in the past 5 years				
Never	327 (21.2)	77 (22.4)	100 (24.7)	70 (25.3)
< Weekly	817 (52.9)	167 (48.5)	194 (47.9)	148 (53.4)
⩾Weekly	401 (26.0)	100 (29.1)	111 (27.4)	59 (21.3)
Ever use of PPI or H_2 blocker	390 (25.5)	193 (53.6)	206 (48.8)	125 (41.7)

*One standard drink is equivalent to 10 g of alcohol.
†Distributions are for all participants with complete data used in the multivariate analysis.

Derivation of variables for analysis

Participants who reported no symptoms of either heartburn or acid reflux during any age period were defined as never having GOR symptoms; all other participants were assigned a GOR symptom frequency equal to the frequency of either heartburn or acid reflux, whichever was the highest. We collapsed the frequency of symptoms into three categories (''never'', ''less than weekly'' and ''at least weekly'') for analysis. Duration of GOR symptoms was calculated as the difference between the reference age and the lower boundary of the age interval in which regular (ie, at least weekly) GOR symptoms were reported for the first time. Body mass index (BMI) was calculated by dividing the weight, in kilograms, by the square of height, in metres. We obtained the lifetime smoking dose in pack-years by summing the smoking dose over each decade of life, calculated by multiplying the decade specific smoking intensity during that decade (cigarettes/day) by the number of days of smoked per week and the smoking duration within that decade.

Statistical analysis

Our primary aim was to measure the relative risk of oesophageal cancer associated with GOR symptoms, and then to assess the effect of potential modifiers. We fitted multivariable logistic regression models to calculate the odds ratios (OR) and the 95% confidence intervals (95% CIs) for the association between GOR symptoms and the three cancer outcomes. We first analysed the frequency of GOR symptoms at four different age intervals (10–19, 20–29, 30–49 and 50–79 years) to examine whether the risk estimates varied with symptoms at different stages of life. Thereafter, we focused principally on the frequency of GOR symptoms reported by each participant during the questionnaire age interval coinciding with 10 years before the reference age. This historic period of exposure was selected to minimise erroneous reporting of cancer symptoms among cases and because of the likely long latency of effect of acid exposure.

Base models included terms only for age and sex, to which we added terms for education, smoking, use of aspirin/NSAIDs in the past 5 years, BMI and alcohol consumption. The matching variable, state of residence, was included in early models but made no difference to any results and hence was dropped. We examined potential statistical interactions between GOR symptoms and smoking, aspirin/NSAIDs use in the past 5 years and other medications by including relevant multiplicative terms in the multivariate model. We also derived measures of combined exposure by cross-classifying each participant according to their GOR symptom frequency and their level of exposure to the potential modifiers (viz. smoking, aspirin/NSAIDs, and acid suppressant medications). We estimated the relative risks associated with exposure to GOR symptoms alone, potential modifiers alone, and both. From these risk estimates, we calculated the synergy index (*S*), which compares the observed excess risk for the combined exposure category relative to the expected excess risk assuming that GOR and the potential modifiers are independent risk factors under an additive model.[19] All analyses were conducted in SAS (V9) and all significance tests were two sided test at $\alpha = 0.05$.

Table 2 Adjusted* risk estimates for the association between GOR symptoms and OAC, GOJAC and OSCC

	Controls	OAC		GOJAC		OSCC	
Frequency of GOR symptoms	**n**	**n**	**OR (95% CI)**	**n**	**OR (95% CI)**	**n**	**OR (95% CI)**
10 years before the reference age†							
Never symptoms	686	74	1.0 (ref)	113	1.0 (ref)	129	1.0 (ref)
< Weekly	681	125	1.6 (1.1 to 2.2)	144	1.2 (0.9 to 1.6)	73	0.6 (0.5 to 0.9)
⩾Weekly	178	145	6.4 (4.6 to 9.1)	148	4.6 (3.3 to 6.3)	75	2.2 (1.5 to 3.2)
Aged 10–19 years							
Never symptoms	526	55	1.0 (ref)	82	1.0 (ref)	108	1.0 (ref)
< Weekly	129	37	3.0 (1.8 to 4.8)	46	2.4 (1.6 to 3.7)	18	0.8 (0.5 to 1.5)
⩾Weekly	22	22	10.5 (5.1 to 21.6)	15	4.8 (2.3 to 10.3)	7	2.2 (0.8 to 5.7)
No symptoms‡	870	231	2.6 (1.9 to 3.6)	263	2.1 (1.6 to 2.8)	146	0.9 (0.6 to 1.2)
Aged 20–29 years							
Never symptoms	526	55	1.0 (ref)	82	1.0 (ref)	108	1.0 (ref)
< Weekly	335	82	2.5 (1.7 to 3.7)	86	1.7 (1.2 to 2.4)	39	0.7 (0.4 to 1.0)
⩾Weekly	59	47	7.4 (4.4 to 12.4)	39	4.4 (2.7 to 7.4)	18	1.9 (1.0 to 3.6)
No symptoms‡	626	161	2.5 (1.8 to 3.6)	199	2.2 (1.7 to 3.0)	114	0.9 (0.7 to 1.3)
Aged 30–49 years							
Never symptoms	518	55	1.0 (ref)	82	1.0 (ref)	108	1.0 (ref)
< Weekly	539	114	2.0 (1.4 to 2.9)	128	1.5 (1.1 to 2.1)	67	0.7 (0.5 to 1.0)
⩾Weekly	127	92	6.4 (4.3 to 9.8)	85	4.5 (3.1 to 6.7)	34	1.6 (1.0 to 2.6)
No symptoms‡	340	83	2.6 (1.8 to 3.9)	111	2.5 (1.8 to 3.5)	70	0.9 (0.6 to 1.3)
Aged 50–79 years							
Never symptoms	428	51	1.0 (ref)	75	1.0 (ref)	105	1.0 (ref)
< Weekly	596	111	1.6 (1.1 to 2.4)	134	1.4 (1.0 to 1.9)	58	0.4 (0.3 to 0.6)
⩾Weekly	169	137	6.9 (4.7 to 10.2)	138	5.0 (3.5 to 7.1)	82	2.2 (1.5 to 3.2)
No symptoms‡	80	17	2.0 (1.1 to 3.8)	14	1.2 (0.6 to 2.2)	17	0.9 (0.5 to 1.6)

*Adjusted for age, sex, further studies, BMI, smoking, alcohol intake and aspirin/NSAIDs use in the past 5 years. Some data were missing for the covariates adjusted in the model.
†Average age (years) for each category of GOR symptom frequency (never, < weekly, > weekly) were controls 59.4, 61.0 and 63.3; OAC 63.1, 63.5 and 64.1; GOJAC 61.7, 64.1 and 63.6; and OSCC 65.1, 62.6 and 66.3.
‡Symptoms were present at other age intervals.
GOJAC, gastro-oesophageal junction adenocarcinoma; OAC, oesophageal adenocarcinoma; OSCC, oesophageal squamous cell carcinoma.

Table 3 Adjusted* risk estimates for the association between combined exposure to GOR and smoking, and OAC, GOJAC and OSCC

	Cumulative smoking history					
	Never smokers		1–29 pack-years		30+ pack-years	
	Controls/cases	OR (95% CI)	Controls/cases	OR (95% CI)	Controls/cases	OR (95% CI)
OAC						
All participants:	702/88	1.0 (ref)	582/137	1.5 (1.1 to 2.1)	261/119	2.3 (1.6 to 3.3)
By frequency of GOR symptoms†:						
Never	327/20	1.0 (ref)	245/27	1.5 (0.8 to 2.8)	114/27	2.5 (1.3 to 4.7)
<Weekly	300/34	1.6 (0.9 to 2.9)	273/48	2.2 (1.2 to 4.0)	108/43	4.1 (2.2 to 7.6)
⩾Weekly	75/34	6.8 (3.6 to 12.9)	64/62	11.1 (6.0 to 20.4)	39/49	12.3 (6.3 to 24.0)
GOJAC						
All participants:	702/90	1.0 (ref)	582/173	2.1 (1.5 to 2.9)	261/142	3.0 (2.2 to 4.3)
By frequency of GOR symptoms†:						
Never	327/30	1.0 (ref)	245/49	2.1 (1.2 to 3.4)	114/34	2.7 (1.5 to 4.7)
<Weekly	300/32	1.1 (0.6 to 1.8)	273/63	2.3 (1.4 to 3.7)	108/49	4.0 (2.3 to 6.8)
⩾Weekly	75/28	4.3 (2.4 to 7.8)	64/61	9.2 (5.4 to 15.8)	39/59	13.5 (7.5 to 24.5)
OSCC						
All participants:	702/72	1.0 (ref)	582/107	2.5 (1.7 to 3.6)	261/100	3.9 (2.6 to 6.0)
By frequency of GOR symptoms†:						
Never	327/34	1.0 (ref)	245/50	2.4 (1.5 to 4.1)	114/45	3.6 (2.1 to 6.4)
<Weekly	300/20	0.7 (0.4 to 1.3)	273/31	1.5 (0.8 to 2.5)	108/22	2.5 (1.3 to 4.7)
⩾Weekly	75/18	1.8 (0.9 to 3.4)	64/24	6.0 (3.1 to 11.7)	39/33	9.2 (4.7 to 18.1)

*Adjusted for age, sex, further studies, body mass index, alcohol intake and aspirin/NSAIDs use in the past 5 years.
†Symptoms reported in the age interval 10 years prior to the reference age.
CI, confidence interval; GOJAC, gastro-oesophageal junction; GOR, gastro-oesophageal reflux; OAC, oesophageal adenocarcinoma; OR, odds ratio; OSCC, oesophageal squamous cell carcinoma.

RESULTS

Demographic and GOR distribution

The distribution of demographic characteristics among cases and controls are presented in table 1. Cases were less likely than controls to be university educated and more likely to be ever smokers. Higher proportions of OAC and GOJAC cases were obese (BMI ⩾30) compared to controls, whereas the opposite was observed for OSCC cases. Controls were slightly more likely to report ever having used aspirin/NSAIDs than cases. Among controls, use of aspirin/NSAIDs was more common among those reporting frequent reflux symptoms compared to those reporting no reflux symptoms. Use of acid suppressant medications (H_2 blockers, PPIs) was reported by substantially higher proportions of cases than controls.

Sixty-seven per cent of controls reported ever having experienced GOR symptoms compared to 84% of OAC and 79% of GOJAC cases. The proportion ever having GOR symptoms was lower among OSCC patients. The frequency of GOR symptoms generally increased with each successive age category for each of the case and control groups (table 2). OAC cases were more likely to report at least weekly GOR symptoms at all ages.

Overall risk estimates associated with GOR symptoms

We observed significant 2- to 3-fold increases in the risk of OAC (OR, 2.7; 95% CI, 2.0 to 3.8) and GOJAC (OR, 2.1; 95% CI, 1.6 to 2.8) among those who had ever experienced GOR symptoms, but not for OSCC (OR, 0.9; 95% CI, 0.7 to 1.2). While the patterns of risk associated with GOR symptoms at different age intervals were consistent for all three cancers, the magnitudes of the relative risks of OAC were higher for those having GOR symptoms at earlier ages (table 2). People reporting at least weekly GOR symptoms after age 20 years had 6- to 7-fold elevations in risk for OAC. Those reporting at least weekly GOR symptoms before age 20 had approximately 10-fold increased risks of this cancer (OR, 10.5; 95% CI, 5.1 to 21.6). The overall risks of OAC and GOJAC among people with at least weekly GOR symptoms in the age category 10 years prior to diagnosis were increased by more than 6-fold (OR, 6.4; 95% CI, 4.6 to 9.1) and 4-fold (OR, 4.6; 95% CI, 3.3 to 6.3) respectively (table 2). In contrast, modest 2-fold elevations in risk of OSCC were observed for people reporting frequent GOR symptoms at all ages, including in the age category the past 10 years.

Combined effects of GOR symptoms and smoking

The risk estimates for GOR were not materially affected by adjusting for smoking, and vice versa, nor were the multiplicative interaction terms statistically significant. However, when interaction was assessed by comparing relative risks for smoking alone, GOR alone and both smoking and GOR, we observed departures from simple additivity. Thus those who reported a 30+ pack-years smoking history but no GOR symptoms experienced relative risks of 2.5 for OAC, 2.7 for GOJAC and 3.6 for OSCC (table 3). Among never smokers, those who reported at least weekly symptoms of GOR had markedly elevated relative risks of OAC and GOJAC (table 3). Relative risks due to the combined effects of GOR and smoking were 60% higher than expected under simple additive models for OAC (*S*, 1.6; 95% CI, 0.8 to 3.0), 150% higher for GOJAC (*S*, 2.5; 95% CI, 1.3 to 4.9) and 140% higher for OSCC (*S*, 2.4; 95% CI, 1.1 to 5.3).

Combined effect of GOR symptoms and aspirin/NSAIDs use

Regular use of aspirin/NSAIDs in the 5 years prior to diagnosis was associated with significant risk reductions of around 40% for all three cancers (table 4). Multiplicative interaction terms for aspirin/NSAID use and GOR were not statistically significant for any type of oesophageal cancer (p values for

Table 4 Adjusted* risk estimates for the association between combined exposure to GOR symptoms and aspirin/NSAIDs use and OAC, GOJAC and OSCC

	Frequency of use of aspirin/NSAIDs‡					
	Never used		<Once a week		At least weekly	
	Controls/cases	OR (95% CI)	Controls/cases	OR (95% CI)	Controls/cases	OR (95% CI)
OAC						
All participants:	327/77	1.0 (ref)	817/167	0.8 (0.6 to 1.1)	401/100	0.6 (0.4 to 0.9)
By frequency of GOR symptoms†:						
Never	182/17	1.0 (ref)	349/37	1.2 (0.7 to 2.3)	155/20	1.0 (0.5 to 2.0)
<Weekly	120/24	2.1 (1.0 to 4.3)	393/66	1.6 (0.9 to 2.9)	168/35	1.6 (0.8 to 3.0)
⩾Weekly	25/36	13.9 (6.5 to 30.0)	75/64	6.7 (3.5 to 12.5)	78/45	4.8 (2.5 to 9.2)
GOJAC						
All participants:	327/100	1.0 (ref)	817/194	0.8 (0.6 to 1.0)	401/111	0.6 (0.4 to 0.8)
By frequency of GOR symptoms†:						
Never	182/27	1.0 (ref)	349/62	1.2 (0.7 to 2.0)	155/24	0.8 (0.4 to 1.4)
<Weekly	120/35	1.9 (1.1 to 3.4)	393/71	1.1 (0.7 to 1.8)	168/38	1.1 (0.6 to 1.9)
⩾Weekly	25/38	8.5 (4.3 to 16.9)	75/61	4.6 (2.7 to 8.0)	78/49	3.1 (1.8 to 5.6)
OSCC						
All participants:	327/70	1.0 (ref)	817/148	1.1 (0.8 to 1.5)	401/59	0.6 (0.4 to 0.9)
By frequency of GOR symptoms†:						
Never	182/38	1.0 (ref)	349/69	1.2 (0.7 to 1.9)	155/22	0.6 (0.3 to 1.1)
<Weekly	120/16	0.7 (0.3 to 1.3)	393/37	0.6 (0.4 to 1.1)	168/20	0.5 (0.3 to 1.0)
⩾Weekly	25/16	2.8 (1.3 to 6.2)	75/42	2.7 (1.5 to 4.8)	78/17	1.0 (0.5 to 2.0)

*Adjusted for age, sex, further studies, body mass index, alcohol intake and smoking.
†Symptoms reported in the age interval 10 years prior to the reference age.
‡Frequency of use in the five years prior to the diagnosis.
CI, confidence interval; GOJAC, gastro-oesophageal junction; GOR, gastro-oesophageal reflux; NSAID, non-steroidal anti-inflammatory drug; OAC, oesophageal adenocarcinoma; OR, odds ratio; OSCC, oesophageal squamous cell carcinoma.

interaction were 0.21, 0.12, 0.44 for OAC, GOJAC and OSCC, respectively). However, in analyses of combined exposure to GOR symptoms and aspirin/NSAIDs (table 4), it can be seen that the risks of OAC and GOJAC were positively associated with frequency of GOR symptoms within all three categories of aspirin/NSAIDs intake (never; <1/week; ⩾1/week). However, the risks of OAC and GOJAC associated with at least weekly GOR symptoms were markedly lower among the regular aspirin/NSAIDs users compared to never users (OAC: OR, 4.8 vs 13.9; GOJAC: OR, 3.1 vs 8.5, table 4). These relative risks for combined exposure were 70% lower than expected under the additive model (*S*, 0.3; 95% CI, 0.1 to 0.7 for both OAC and GOJAC). While the risk of OSCC associated with frequent GOR symptoms diminished to null among regular users of aspirin/NSAIDs, there was no evidence of synergy. When the analysis for aspirin and NSAIDs were performed independently and exclusively, there were some fluctuations in the estimates of risks due to smaller sample size however the pattern of effects remained the same for both aspirin and NSAID.

Combined effect of GOR symptoms and acid suppressants

Use of acid suppressant medications was significantly more common among all groups of cases than population controls (see overall effects, table 5). As expected, these medications were used predominantly, although not exclusively, by people reporting GOR symptoms. We found no evidence that the risks of oesophageal cancer associated with GOR symptoms were modified by use of acid suppressants. Indeed, among those reporting at least weekly symptoms of reflux, the risks of OAC, GOJAC and OSCC were very similar for acid suppressant users and non-users (OAC: OR, 7.8 vs 5.0; GOJAC: OR, 4.9 vs 5.0; OSCC: OR, 2.7 vs 2.3) and the synergy index for the combined effect were not statistically significant. As our results may have been confounded by medication use due to symptoms shortly before diagnosis, we repeated our analysis in the subset of people where medication use in the past one to five years was available and reached the same conclusion (data not shown).

DISCUSSION

We have explored the effect of GOR symptoms on the risks of the three most common subtypes of oesophageal cancer. We found consistently increasing risks of OAC and GOJAC with increasing frequency of GOR symptoms. Whilst no such trend was observed for OSCC, we did find an increased risk of OSCC among those who reported at least weekly frequent GOR symptoms, albeit of markedly lesser magnitude than those observed for OAC and GOJAC. Most importantly, we found evidence that smoking and use of aspirin/NSAIDs modified the effects of acid reflux in different directions. Specifically, whereas risks of OAC and GOJAC associated with GOR symptoms were higher among smokers compared to never smokers, they were significantly lower among regular users of aspirin or NSAIDs. We found no evidence that regular use of acid-suppressants modified the risk of OAC and GOJAC associated with frequent GOR symptoms.

Our finding of greater than 2-fold increase in the risk for OAC among those reporting ever having GOR symptoms is consistent with the reports from previous case control studies.[5 6] Similarly, the 7-fold risk of OAC we observed among those reporting at least weekly GOR symptoms also agrees with previously reported risk estimates.[6 20 21] Few studies have reported on associations between GOR symptoms and OSCC, and while we found a modest positive association, this was not observed in previous population based case–control studies conducted in the USA and Sweden.[6 20]

Table 5 Adjusted* risk estimates for the association between combined GOR symptoms and acid suppressant use and OAC, GOJAC and OSCC

	Frequency of use of acid suppressants			
	Never used		Ever used	
	Controls/cases	OR (95% CI)	Controls/cases	OR (95% CI)
OAC				
Overall effect:	1129/157	1.0 (ref)	385/188	3.3 (2.5 to 4.2)
By frequency of GOR symptoms†:				
Never	581/57	1.0 (ref)	74/17	1.9 (1.0 to 3.5)
<Weekly	487/60	1.1 (0.8 to 1.7)	194/65	3.1 (2.1 to 4.7)
⩾Weekly	61/40	5.3 (3.2 to 9.0)	117/105	7.8 (5.2 to 11.8)
GOJAC				
Overall effect:	1129/212	1.0 (ref)	385/194	2.5 (2.0 to 3.2)
By frequency of GOR symptoms†:				
Never	581/89	1.0 (ref)	74/24	1.9 (1.1 to 3.2)
<Weekly	487/75	0.9 (0.7 to 1.3)	194/69	2.1 (1.5 to 3.1)
⩾Weekly	61/48	4.9 (3.0 to 7.8)	117/100	5.0 (3.4 to 7.2)
OSCC				
Overall effect:	1129/163	1.0 (ref)	385/114	2.0 (1.5 to 2.7)
By frequency of GOR symptoms†:				
Never	581/96	1.0 (ref)	74/32	2.4 (1.4 to 4.0)
<Weekly	487/41	0.6 (0.4 to 0.9)	194/32	1.1 (0.7 to 1.7)
⩾Weekly	61/26	2.3 (1.3 to 4.1)	117/48	2.7 (1.7 to 4.1)

*Adjusted for age, sex, further studies, body mass index, alcohol intake and aspirin/NSAIDs use in the past 5 years.
†Symptoms reported in the age interval 10 years prior to the reference age.
CI, confidence interval; GOJAC, gastro-oesophageal junction; GOR, gastro-oesophageal reflux; OAC, oesophageal adenocarcinoma; OR, odds ratio; OSCC, oesophageal squamous cell carcinoma.

Smoking has long been known to be associated with increased frequency of GOR symptoms[22] and the independent effects of these exposures on OAC have been previously documented;[5 20 23 24] however, little was known about the effects of combined exposure. Our data suggest that people with frequent GOR symptoms who also smoke heavily have more than 1.5 times higher risks of OAC and more than two times higher risks of GOJAC and OSCC than would be predicted assuming that the risks of reflux and smoking were simply additive. In previous analyses, we found smoking to be more strongly associated with GOJAC than OAC[13] and here we observed that the effects of combined exposure to smoking and GOR symptoms were also stronger for GOJAC than OAC. Further, we have previously reported the synergistic effects of gastro-oesophageal reflux and obesity on risks of OAC and GOJAC.[4] While we adjusted for body mass index in all models, we cannot exclude the possibility that the complex patterns of synergy that we have identified in this set of analyses may differ according to adiposity. To identify and measure such multi-level interactions with precision would require a substantially larger sample, as might be achieved with a pooled analysis of existing datasets.

The biological mechanisms underpinning the association between gastro-oesophageal reflux and oesophageal cancer are becoming clearer. Chronic reflux of acid and bile into the oesophagus injures the epithelium, inducing cascades of cytokine responses[25] and in turn leading to inflammation and cell proliferation. Experiments conducted in cell lines have demonstrated the genotoxic effects of exposure to physiological levels of acid and bile, including single- and double-strand DNA breaks and oxidative damage.[26–28] In addition, acid in the oesophageal lumen reacts with nitrites in swallowed saliva to generate nitric oxide,[29] a mutagen which has been demonstrated specifically to induce DNA damage in Barrett's oesophagus cell lines.[26 30]

One of the mechanisms by which smoking might enhance the effects of GOR is through inflammatory pathways.[31] Smoking is also known to relax lower oesophageal sphincter tone, leading to prolonged acid exposure[32] which may enhance the effects of GOR and thereby increasing the risk for oesophageal cancer.

The likely chemopreventive role of NSAIDs has been described for many epithelial cancers,[33 34] including oesophageal adenocarcinoma and its precursor Barrett's oesophagus.[15–17 35 36] Our estimates of approximate 40% risk reductions for all oesophageal cancers among frequent users of aspirin/NSAIDs were similar to those estimated by meta-analyses.[16 36] Several previous studies have investigated possible interactions between use of NSAIDs and history of oesophageal disorders (including GOR), with some inconsistency of findings. Linblad *et al*[37] observed greater risk reductions associated with NSAID use among those with upper gastrointestinal disorders, as we did. In contrast, Farrow *et al*[15] and Anderson *et al*[17] reported greater risk reductions among those with no reflux symptoms. Aspirin and NSAIDs reduce the severity of inflammation associated with GOR, which may protect the epithelium from possible carcinogenic sequelae. This phenomenon has been observed in studies of animals with surgically induced reflux, where COX-2 inhibitors reduced the degree of inflammation, progression to Barrett's oesophagus, and eventual adenocarcinoma.[34] Clinical trials in humans are currently under way to test whether aspirin prevents the development of OAC among patient with Barrett's oesophagus, but the results are not yet available.[38] Our data suggest that the possible benefits of aspirin should be greatest in those with the most frequent symptoms of reflux.

In contrast to the reduced risks of OAC and GOJAC associated with use of aspirin or NSAIDs, we found no evidence that use of acid suppressant medications such as PPI or H_2 blockers modified the association between frequent GOR symptoms and OAC or GOJAC. While misclassification of medication history is always possible, our findings of specific associations with one class of medications (NSAIDs) but not others (acid suppressants) would argue against universally biased reporting of medication history. Indeed, for bias to explain our findings, the patterns of association we observed

would require systematic under-reporting by cases of their NSAIDs exposures, but not H_2 or PPI exposure, a pattern of recall we consider unlikely. We cannot exclude the possibility of confounding by indication, whereby patients with frequent reflux symptoms either were not prescribed or otherwise avoided the use of NSAIDs in the years preceding the study, although why this should apply only to cases but not controls is not easy to explain. Use of H_2 blockers alone was shown to have no impact on OAC risk in one previous US study[20] and we observed similar effects when we repeated our analyses restricted to those who used H_2 blockers but not PPIs. While PPI use has been shown to be beneficial with regard to cancer risk in some studies,[39 40] a clinical trial assessing short-term PPI treatment in patients with erosive oesophagitis observed changes in some measures of cellular immunity but found no difference in oxidative DNA damage, suggesting that reflux-induced genotoxicity is not altered by these medications.[41] Our observation of overall higher PPI use among cases than controls may reflect confounding by indication, where PPI use is an indicator for symptom severity. Overcoming this potential bias is difficult using the case–control design; hence caution is required in interpreting such findings.

Strengths of the study include the large sample size, the population-based sampling frame and the very detailed measures of exposure to a broad range of potential causal factors. These data allowed us to explore modifiers of the association between GOR symptoms and oesophageal cancer to an extent not undertaken previously.

Our study experienced a low participation rate among controls, similar to other recent studies; however, the prevalence of at least weekly GOR symptoms in our control population (~12%) was similar to that observed in other population-based studies in Australia,[42] the UK[43] and Sweden.[6] Although recall bias may have occurred, several features suggest that the likely extent is limited. We obtained a detailed lifetime history of reflux, asking for the frequency and severity of symptoms within four discrete age periods. We found that very few participants reported GOR symptoms in early life, and that frequency of GOR symptoms increased with age among cases and controls, as reported in other studies.[8] Moreover, we observed very different risk estimates for OAC and OSCC associated with GOR symptoms, strong evidence against systematic over-reporting among all patients with oesophageal cancer. Our finding of modestly elevated risks of OSCC associated with reflux has not been reported previously, however, and might be interpreted by some as evidence for biased recall. Although we cannot completely exclude this possibility, the patterns of association and subsequent effect modification by smoking and use of NSAIDs, point to an alternative conclusion. Another explanation for the associations with GOR might be "reverse causality". This would occur if symptoms of oesophageal discomfort due to incipient cancer were misreported by cases as GOR. While this might partially explain the higher prevalence of recent GOR symptoms among cases, it is highly unlikely that symptoms from a growing tumour would be experienced at young ages, as we observed among OAC, GOJAC and OSCC cases.

Finally, we identified largely concordant findings in the relations between reflux, smoking and the use of aspirin/NSAIDs and risks of OAC and GOJAC. The overall patterns of association were very similar for these two cancers, although the associations with reflux symptoms appeared consistently stronger for patients with OAC than GOJAC, whereas associations with smoking were stronger for patients with GOJAC than OAC. It is possible that some of these differences in effect may stem from anatomical misclassification of tumours, since there is always uncertainty as to the precise location of origin of bulky tumours in the region of gastro-oesophageal junction.[44] Thus a small proportion of the tumours defined as "GOJ" in this series may have originated in the proximal stomach, which might account for some of the differences in effect that we observed.

In summary, we have demonstrated the importance of GOR as a major risk factor for OAC and GOJAC, and quantified the strength of the association. Further, our data suggest that GOR symptoms might also be associated with OSCC, an association not identified in previous studies. Finally, we have found that the association between GOR symptoms and oesophageal cancer is exacerbated by smoking, and ameliorated by anti-inflammatory medications. Definitive evidence for these effects can only be obtained from experimental designs involving animals (to test possible synergies between smoking and reflux) or humans (to assess the effects of aspirin/NSAIDs among patients with frequent, chronic reflux).

Funding: This study was supported by the Queensland Cancer Fund and the National Health and Medical Research Council (NHMRC) of Australia (Program no. 199600). DW and PW are supported by Research Fellowships from the NHMRC. NP and SS were supported by PhD scholarships from the NHMRC and the Ministry of Health and Medical Education of the Islamic Republic of Iran, respectively. The funding bodies played no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Competing interests: None.

Ethics approval: This study was approved by the Human Research Ethics Committee of the Queensland Institute of Medical Research (Project-ID P399) and all participants gave their written consent to participate.

Authors' contributions: NP performed the statistical analysis and prepared the manuscript. SS assisted in data preparation and interpretation. DW, PW and AG designed the original study and supervised the collection of data. All authors assisted in preparing the manuscript and approved the final version.

Provenance and peer review: Not commissioned; externally peer reviewed.

REFERENCES

1. **Blot WJ,** McLaughlin JK. The changing epidemiology of esophageal cancer. *Semin Oncol* 1999;**26**:2–8.
2. **Botterweck AAM,** Schouten LJ, Volovics A, *et al*. Trends in incidence of adenocarcinoma of the oesophagus and gastric cardia in ten European countries. *Int J Epidemiol* 2000;**29**:645–54.
3. **Hansson LE,** Sparen P, Nyren O. Increasing incidence of both major histological types of esophageal carcinomas among men in Sweden. *Int J Cancer* 1993;**54**:402–7.
4. **Whiteman DC,** Sadeghi S, Pandeya N, *et al*. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. *Gut* 2008;**57**:173–80.
5. **Chow WH,** Finkle WD, McLaughlin JK, *et al*. The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. *JAMA* 1995;**274**:474–7.
6. **Lagergren J,** Bergstrom R, Lindgren A, *et al*. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999;**340**:825–31.
7. **Lagergren J,** Ye W, Bergstrom R, *et al*. Utility of endoscopic screening for upper gastrointestinal adenocarcinoma. *JAMA* 2000;**284**:961–2.
8. **El-Serag HB.** Time trends of gastroesophageal reflux disease: a systematic review. *Clin Gastroenterol Hepatol* 2007;**5**:17–26.
9. **Corley DA,** Kubo A, Zhao W. Abdominal obesity, ethnicity and gastro-oesophageal reflux symptoms. *Gut* 2007;**56**:756–62.
10. **Lagergren J.** Controversies surrounding body mass, reflux, and risk of oesophageal adenocarcinoma. *Lancet Oncol* 2006;**7**:347–9.
11. **Kabat GC,** Ng SK, Wynder EL. Tobacco, alcohol intake, and diet in relation to adenocarcinoma of the esophagus and gastric cardia. *Cancer Causes Control* 1993;**4**:123–32.
12. **Freedman ND,** Abnet CC, Leitzmann MF, *et al*. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *Am J Epidemiol* 2007;**165**:1424–33.
13. **Pandeya N,** Williams GM, Sadhegi S, *et al*. Associations of duration, intensity, and quantity of smoking with adenocarcinoma and squamous cell carcinoma of the esophagus. *Am J Epidemiol* 2008;**168**:105–14.

14. **Smith KJ,** O'Brien SM, Smithers BM, *et al*. Interactions among smoking, obesity, and symptoms of acid reflux in Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:2481–6.
15. **Farrow DC,** Vaughan TL, Hansten PD, *et al*. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev* 1998;**7**:97–102.
16. **Corley DA,** Kerlikowske K, Verma R, *et al*. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. *Gastroenterology* 2003;**124**:47–56.
17. **Anderson LA,** Johnston BT, Watson RG, *et al*. Nonsteroidal anti-inflammatory drugs and the esophageal inflammation–metaplasia–adenocarcinoma sequence. *Cancer Res* 2006;**66**:4975–82.
18. **Sadeghi S,** Bain CJ, Pandeya N, *et al*. Aspirin, nonsteroidal anti-inflammatory drugs, and the risks of cancers of the esophagus. *Cancer Epidemiol Biomarkers Prev* 2008;**17**:1169–78.
19. **Rothman KJ.** *Modern epidemiology*. Boston: Little, Brown, 1986.
20. **Farrow DC,** Vaughan TL, Sweeney C, *et al*. Gastroesophageal reflux disease, use of H2 receptor antagonists, and risk of esophageal and gastric cancer. *Cancer Causes Control* 2000;**11**:231–8.
21. **Wu AH,** Tseng CC, Bernstein L. Hiatal hernia, reflux symptoms, body size, and risk of esophageal and gastric adenocarcinoma. *Cancer* 2003;**98**:940–8.
22. **Zheng Z,** Nordenstedt H, Pedersen NL, *et al*. Lifestyle factors and risk for symptomatic gastroesophageal reflux in monozygotic twins. *Gastroenterology* 2007;**132**:87–95.
23. **Gammon MD,** Schoenberg JB, Ahsan H, *et al*. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst* 1997;**89**:1277–84.
24. **Lagergren J,** Bergstrom R, Lindgren A, *et al*. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. *Int J Cancer* 2000;**85**:340–6.
25. **Yoshida N.** Inflammation and oxidative stress in gastroesophageal reflux disease. *J Clin Biochem Nutr* 2007;**40**:13–23.
26. **Clemons NJ,** McColl KEL, Fitzgerald RC. Nitric oxide and acid induce double-strand DNA breaks in Barrett's esophagus carcinogenesis via distinct mechanisms. *Gastroenterology* 2007;**133**:1198–209.
27. **Jenkins GJS,** Cronin J, Alhamdani A, *et al*. The bile acid deoxycholic acid has a non-linear dose response for DNA damage and possibly NF-kappa B activation in oesophageal cells, with a mechanism of action involving ROS. *Mutagenesis* 2008;**23**:399–405.
28. **Jolly AJ,** Wild CP, Hardie LJ. Sodium deoxycholate causes nitric oxide mediated DNA damage in oesophageal cells. *Free Radical Res* 2009;**43**:234–40.
29. **Suzuki H,** Iijima K, Scobie G, *et al*. Nitrate and nitrosative chemistry within Barrett's oesophagus during acid reflux. *Gut* 2005;**54**:1527–35.
30. **Ishiyama F,** Iijima K, Asanuma K, *et al*. Exogenous luminal nitric oxide exacerbates esophagus tissue damage in a reflux esophagitis model of rats. *Scand J Gastroenterol* 2009;**44**:527–37.
31. **Levitzky YS,** Guo CY, Rong J, *et al*. Relation of smoking status to a panel of inflammatory markers: The Framingham offspring. *Atherosclerosis* 2008;**201**:217–24.
32. **Zimmerman J.** Irritable bowel, smoking and oesophageal acid exposure: an insight into the nature of symptoms of gastro-oesophageal reflux. *Aliment Pharmacol Therap* 2004;**20**:1297–304.
33. **Yang CY,** Meng CL, Liao CL, *et al*. Regulation of cell growth by selective COX-2 inhibitors in oral carcinoma cell lines. *Prostaglandins Other Lipid Mediat* 2003;**72**:115–30.
34. **Buttar NS,** Wang KK, Leontovich O, *et al*. Chemoprevention of esophageal adenocarcinoma by COX-2 inhibitors in an animal model of Barrett's esophagus. *Gastroenterology* 2002;**122**:1101–12.
35. **Duan L,** Wu AH, Sullivan-Halley J, *et al*. Nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric adenocarcinomas in Los Angeles County. *Cancer Epidemiol Biomarkers Prev* 2008;**17**:126–34.
36. **Abnet CC,** Freedman ND, Kamangar F, *et al*. Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: results from a cohort study and a meta-analysis. *Br J Cancer* 2009;**100**:551–7.
37. **Lindblad M,** Lagergren J, Rodriguez LAG. Nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:444–50.
38. **Das D,** Chilton AP, Jankowski JA. Chemoprevention of oesophageal cancer and the AspECT trial. *Recent Results Cancer Res* 2009;**181**:161–9.
39. **Hillman LC,** Chiragakis L, Shadbolt B, *et al*. Effect of proton pump inhibitors on markers of risk for high-grade dysplasia and oesophageal cancer in Barrett's oesophagus. *Aliment Pharmacol Therap* 2008;**27**:321–6.
40. **El-Serag HB,** Aguirre TV, Davis S, *et al*. Proton pump inhibitors are associated with reduced incidence of dysplasia in Barrett's esophagus. *Am J Gastroenterol* 2004;**99**:1877–83.
41. **De Jonge PJF,** Siersema PD, Van Breda SGJ, *et al*. Proton pump inhibitor therapy in gastro-oesophageal reflux disease decreases the oesophageal immune response but does not reduce the formation of DNA adducts. *Aliment Pharmacol Therap* 2008;**28**:127–36.
42. **Watson DI,** Lally CJ. Prevalence of symptoms and use of medication for gastroesophageal reflux in an Australian community. *World J Surg* 2009;**33**:88–94.
43. **Murray L,** Johnston B, Lane A, *et al*. Relationship between body mass and gastro-oesophageal reflux symptoms: The Bristol Helicobacter Project. *Int J Epidemiol* 2003;**32**:645–50.
44. **Rusch VW.** Are cancers of the esophagus, gastroesophageal junction, and cardia one disease, two, or several? *Semin Oncol* 2004;**31**:444–9.

Int. J. Cancer: **123,** 174–180 (2008)

Polymorphisms in MGMT and DNA repair genes and the risk of esophageal adenocarcinoma

James Doecke, Zhen Zhen Zhao, Nirmala Pandeya, Shahram Sadeghi, Mitchell Stark, Adèle C. Green, Nicholas K. Hayward, Penelope M. Webb and David C. Whiteman* for the Australian Cancer Study

Queensland Institute of Medical Research, Brisbane, Queensland, Australia

Rates of adenocarcinoma of the esophagus (EAC) and esophago-gastric junction (EGJAC) have increased rapidly in recent decades. The primary risk factors, gastro-esophageal acid reflux and smoking, are potentially genotoxic through the generation of *N*-nitroso compounds. The DNA repair protein O^6-methylguanine-DNA methyltransferase (MGMT) is the major cellular defense against alkylating DNA damage. We compared patients with EAC ($n = 263$) or EGJAC ($n = 303$) with matched population controls ($n = 1{,}337$) for the frequency of 5 *MGMT* single nucleotide polymorphisms (SNPs) (rs12269324, rs12268840, L84F, I143V, K178R), as well as SNPs in DNA repair genes *ERCC1* (N118N), *XRCC1* (Q399R) and *XPD* (K751Q). Relative risks were estimated using multivariable logistic regression. Potential biological interaction was assessed through the synergy index *S*. Each *MGMT* SNP conferred increased risks of EAC but not EGJAC; strongest associations were found for the 2 variant *MGMT* alleles rs12268840 and I143V ($p = 0.005$ and $p < 0.001$, respectively). Homozygous carriers of *MGMT* rs12268840 with frequent acid reflux had significantly higher risks of EAC (OR 15.5, 95% CI 5.8–42) than expected under an additive model, consistent with biological interaction ($S = 3.3$, 95% CI 1.1–10). Modest, nonsignificant interactions with smoking were also observed. Homozygous variant *ERCC1* genotype was associated with reduced risks of EAC (OR 0.6, 95% CI 0.4–1.1), while the homozygous variant *XRCC1* genotype conferred higher risks of EGJAC (OR 1.6, 95% CI 1.1–2.4). No associations with EAC or EGJAC were observed with *XPD* (rs13181). In summary, *MGMT* SNPs are associated with increased risks of EAC. Exposure to acid reflux, and possibly smoking, confer markedly higher risks among homozygous variant genotype carriers.

Key words: MGMT; single nucleotide polymorphism; esophageal adenocarcinoma

Adenocarcinomas of the esophagus (EAC) and esophago-gastric junction (EGJAC) have been rising in incidence in many countries around the world[1–3]; in some populations the rate of increase has been faster than for any other major cancer.[4] In Australia, the age-standardized rate of EAC has risen from 4 per million person-years in 1982 to 22 per million person-years in 2002 (Australian Institute of Health and Welfare, National Cancer Statistics Clearing House). Epidemiological studies have consistently demonstrated that gastro-esophageal acid reflux, obesity and smoking are the principal risk factors for these cancers,[5,6] although the precise molecular pathways through which they act remain to be defined. There seems little doubt individuals differ in their sensitivity to the effects of these factors since the vast majority of people exposed to acid reflux, smoking or obesity do not develop EAC or EGJAC.

In animal models, EAC can be induced by administering *N*-nitroso compounds to the esophagus, and it is hypothesized that a similar mechanism occurs in humans through the mixing of salivary nitrites and gastric acid.[7,8] Briefly, dietary nitrates from green leafy vegetables are absorbed in the small intestine and are largely excreted in the urine, however about 30% of the nitrate load is concentrated by the salivary glands and secreted into the oral cavity. Here, bacteria colonizing the dorsum of the tongue rapidly reduce the nitrates (NO_3) to nitrites (NO_2). Upon encountering

Abbreviations: BMI, body mass index; CI, confidence interval; N, number; OR, odds ratio; RR, relative risk; %, percentage.

The first two authors contributed equally to this work.

Grant sponsor: National Health and Medical Research Council of Australia (NHMRC); Grant number: 199600; Grant sponsors: Queensland Cancer Fund, Ministry of Health and Medical Education of IR Iran.

The Australian Cancer Study Oesophageal Cancer: Investigators: D. C. Whiteman, P. M. Webb, A. C. Green, N. K. Hayward, P. G. Parsons, and D. M. Purdie, Division of Population Health and Human Genetics, Queensland Institute of Medical Research, Brisbane, Australia.

Clinical Collaborators: B. M. Smithers and D. Gotley, Department of Surgery, University of Queensland, Brisbane, Australia; A. Clouston, Envoi Pathology, Brisbane, Australia; I. Brown, S&N Pathology, Brisbane, Australia.

Project Manager: S. Moore, Division of Population Health and Human Genetics, Queensland Institute of Medical Research, Brisbane, Australia.

Database: K. Harrap and T. Sadkowski, Division of Population Health and Human Genetics, Queensland Institute of Medical Research, Brisbane, Australia.

Research Nurses: S. O'Brien, E. Minehan, L. Terry, and M. Connard, Division of Population Health and Human Genetics, Queensland Institute of Medical Research, Brisbane, Australia; D. Roffe, Department of Surgery, Royal Adelaide Hospital, Adelaide, Australia; S. O'Keefe, St John of God Hospital, Geelong, Australia; S. Lipshut, F. Walker, and L. Bowes, Peter MacCallum Cancer Center, Melbourne, Australia; G. Connor, Department of Surgery, Sir Charles Gairdner Hospital, Perth, Australia; H. Berry, Department of Surgery, Royal North Shore Hospital, Sydney, Australia; J. Thomas, GIAST Clinic, Mater Private Medical Center, Brisbane, Australia; M. Malt, Canberra, Australia; J. White, Royal Adelaide Hospital, Adelaide, Australia.

Clinical Contributors: Australian Capital Territory: C. Mosse and N. Tait, Calvary Hospital, Canberra, Australia. New South Wales: C. Bambach, North Shore Medical Centre, Sydney, Australia; A. Biankan, Garvan Institute of Medical Research, Sydney, Australia; R. Brancatisano, Institute of Weight Control, Sydney, Australia; M. Coleman, St Vincent's Clinic, Sydney, Australia; M. Cox, Penrith, Australia; S. Deane, John Hunter Hospital, Newcastle, Australia; G. L. Falk, Concord Hospital, Sydney, Australia; J. Gallagher and D. Storey, Royal Prince Alfred Hospital, Sydney, Australia; M. Hollands, Castle Hill Day Surgery, Sydney, Australia; T. Hugh, G. Smith, and R. Smith, Royal North Shore Hospital, Sydney, Australia; D. Hunt and J. Jorgensen, St George Private Hospital, Sydney, Australia; C. Martin, Nepean Hospital, Sydney, Australia; M. Richardson, Blacktown, Australia. Queensland: J. Avramovic and J. Masson, Townsville General Hospital, Townsville, Australia; J. Croese and S. Fairley, Townsville, Australia; J. D'Arcy, Sunshine Coast Private Hospital Specialist Centre, Nambour, Australia; J. Hansen, Nambour Hospital, Nambour, Australia; L. Nathanson, B. O'Loughlin and M. Windsor, Royal Brisbane Hospital, Brisbane, Australia; L. Rutherford, Pacific Private Clinic, Gold Coast, Australia; R. Turner, Cairns Base Hospital, Brisbane, Australia; South Australia: J. Bessell, Southern Gastric Services, Adelaide, Australia; P. Devitt, G. Jamieson, Royal Adelaide Hospital, Adelaide, Australia; D. Watson, Flinders Medical Centre, Adelaide, Australia. Victoria: S. Blamey and J. Gribben, Monash Medical Center, Melbourne, Australia; A. Boussioutas and R. Thomas, Peter MacCallum Cancer Centre, Melbourne, Australia; R. Cade, Box Hill Hospital, Melbourne, Australia; G. Crosthwaite, Melbourne, Australia; I. Faragher, Western Hospital, Melbourne, Australia; G. Hebbard, B. Mann, and B. Millar, Royal Melbourne Hospital, Melbourne, Australia; G. Kiroff, St John of God Hospital, Geelong, Australia; P. O'Brien, Alfred Hospital, Melbourne, Australia; S. Woods, Cabrini Hospital, Melbourne, Australia; Western Australia: S. Archer, Royal Perth Hospital, Perth, Australia; K. Faulkner and J. Hamdorf, St John of God Health Centre, Perth, Australia.

***Correspondence to:** Division of Population Studies and Human Genetics, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Queensland 4029, Australia. Fax: +61-7-3845-3503.
E-mail: david.whiteman@qimr.edu.au

Received 15 October 2007; Accepted after revision 7 December 2007
DOI 10.1002/ijc.23410
Published online 3 April 2008 in Wiley InterScience (www.interscience.wiley.com).

gastric acid, the nitrites in saliva are converted to nitrous acid, nitric oxide and other nitrosating species.[9] This reaction occurs at the gastro-esophageal junction in "healthy" people, but occurs in the esophagus among those suffering gastric acid reflux.[8,10] *N*-nitroso compounds are known to be mutagenic and carcinogenic, particularly through their ability to alkylate DNA at the O^6 position of guanine.[11] Tobacco smoke is also a potent source of nitrosamine compounds, several of which are established carcinogens,[12,13] and these are also likely to be present in the esophagus.

The major defense against alkylating mutations is from O^6-methylguanine-DNA methyltransferase (MGMT), a 207 amino acid DNA repair protein that transfers potentially carcinogenic O^6 alkylation adducts from the DNA to a cysteine residue of MGMT.[14,15] For each adduct removed, an MGMT molecule is inactivated, hence the capacity for each cell to repair DNA depends upon the total number of MGMT molecules in the cell. Single nucleotide polymorphisms (SNPs) in 2 regions of the *MGMT* gene have been associated with up to 10-fold difference in expression between individuals,[16] leading to speculation that *MGMT* SNPs may be associated with increased risks of cancer, especially among those exposed to alkylating mutagens.

Previous investigations have reported modest associations between *MGMT* polymorphisms and esophageal squamous cell carcinoma,[17] lung cancer,[18] melanoma[19] and cancers of the upper-aero digestive tract,[20] and while a small number of studies have investigated associations between other DNA repair genes (notably *XPD*, *XRCC1* and *ERCC1*) and risks of EAC or EGJAC,[21–23] none have investigated associations between *MGMT* polymorphisms and these cancers.

Here, we report the findings from an Australian population-based case-control study in which we tested the hypothesis that polymorphisms in *MGMT, XPD, XRCC1* and *ERCC1* are associated with increased risks of EAC and EGJAC. We postulated that the risks associated with variant alleles of these genes would be higher among those exposed to potentially genotoxic factors (specifically, gastro-esophageal acid reflux and tobacco smoke) compared to those not exposed to these factors.

Material and methods

Approval to undertake the study was obtained from the human research ethics committees of the Queensland Institute of Medical Research and participating hospitals throughout Australia. Written informed consent was obtained from all participants.

Study participants

Full details of recruitment and data collection have been published previously.[24] Briefly, patients eligible for inclusion were those aged 18–79 years with a histologically confirmed adenocarcinoma of the esophagus or EGJAC diagnosed from July 1, 2001 (in Queensland) or July 1, 2002 (in the other mainland states of Australia) until June 30, 2005. The principal mode of ascertainment was via major treatment centers; those missed at these centers were identified by state-based cancer registries (notification of cancer is mandatory). Anatomical sites of adenocarcinomas were categorized according to the WHO classification[25] as either "esophageal" or "EGJAC" tumors.

We identified 1,610 eligible patients attending treatment centers during the study period, for whom doctors refused contact with 71 and 167 died before consent could be obtained. A further 181 patients were excluded because they were too ill, mentally incapable, could not read or write in English or were uncontactable. The remaining 1,191 patients were invited to participate, and of these, 928 (78% of those invited) agreed to take part. A further 739 alive and eligible patients were identified through the cancer registries and of these, treating doctors refused contact for 84 patients, 37 patients were incapable of taking part and 232 patients were unable to be contacted. Two hundred and fifty three of the remaining 386 cancer registry patients agreed to take part (66% of those registry patients invited). In total, 1,181 patients with esophageal cancer consented to take part in the study (928 clinic and 253 registry patients).

Potential controls were randomly selected from the Australian Electoral Roll (enrolment is compulsory) matched within strata of age and state to the cases. We aimed for similar numbers of male cases and controls in each stratum of age and state; female controls were intentionally oversampled at all ages to permit simultaneous enrolment in a case-control study of ovarian cancer.[26] Of 3,258 potentially eligible control participants, 41 could not be contacted and 175 were excluded because they were deceased, too ill, or unable to read or write in English. Of 3,042 controls meeting the inclusion criteria, 1,680 (55%) gave their consent to take part. Completed questionnaires were returned by 1,580 controls (48% of all potentially eligible controls selected from the roll).

Data collection

Information was collected via self-completed questionnaires asking about each participant's education, height and weight 1 year ago (1 year before diagnosis for cases). Participants were asked whether, over their whole life, they had ever smoked more than 100 cigarettes, cigars, or pipes; positive responses elicited further questions about ages started and stopped smoking and typical daily consumption. We derived the number of pack-years of tobacco exposure by dividing the number of cigarettes smoked daily by 20 and multiplying by the total number of years smoked. For analysis, "never smokers" were the reference category and "ever smokers" were categorised according to total pack-years of smoking. We asked participants to report the frequency with which they consumed different classes of alcohol (low alcohol beer, regular beer, white wine, red wine, port/sherry and spirits/liqueurs) between ages 20–29, 30–49 and >50 years, as applicable. Total alcohol consumption was summed across all age groups for all types of alcohol, from which we calculated a weighted average number of standard drinks (10 g ethanol) consumed per week between age 20 years and current age. We assessed the frequency of symptoms of gastro-esophageal reflux 10 years before diagnosis, defined as the presence of heartburn (a burning pain behind the breastbone after eating) or acid reflux (a sour taste from acid or bile rising up into the mouth or throat). For analysis, we used the highest reported frequency for either symptom and defined "frequent symptoms" as those occurring at least weekly.[27,28] We calculated the body mass index (BMI) by dividing weight in kilograms by the square of height in meters.

Participants provided whole blood samples for genotyping. Facilities for the systematic collection of blood became available 6 months after the study commenced and no attempt was made to recontact those participants who had already completed data collection.

Single nucleotide polymorphisms

In total, 5 SNPs in the *MGMT* gene were tested, including 2 in intron 1 (rs12269324, and rs12268840), 1 in exon 3 (L84F; rs12917) and 2 in exon 5 (I143V; two in exon 5 (I143V; rs2308327 and K178R; rs2308327). In addition, we tested SNPs from other DNA repair genes that had previously been investigated for esophageal adenocarcinoma including *ERCC1* exon 3 (N118N; rs11615); *XPD* exon 23 (K751Q; rs13181); and *XRCC1* exon 10 (Q399R; rs25487). All SNPs were tested for Hardy Weinberg equilibrium (HWE) prior to statistical analysis. As *MGMT* SNPs I143V and K178R were in complete linkage disequilibrium (LD),[15] only data for I143V are reported here. Both wild type and variant DNA sequences for SNP rs12268840 were assessed for aberrant DNA binding *in silico* via the transcription element search software (TESS).

Genotyping assays

SNP typing was conducted using the Sequenom™ iPLEX™ protocol (Sequenom, San Diego, CA). 2.5 μL PCR reactions were performed in standard 384-well plates including 10 ng genomic DNA, 0.5 units of Taq polymerase (HotStarTaq, Qiagen, Valencia, CA), 500 μmol of dNTPs and 100 nmol of both forward and

reverse PCR primers. Thermocycling conditions within the ABI-9700 (Applied Biosystems, Foster City, USA) consisted of an initial 15-min denaturation at 94°C, followed by 45 cycles of 20-sec denaturing at 94°C, 30-sec annealing at 56°C, and 60-sec extension at 72°C. PCR products were purified by incubation at 37°C (using 0.15 units of Shrimp Alkaline Phosphatase) for 30 min followed by a 5-min inactivation step at 85°C. A primer extension reaction mixture including 0.1 μL of a 10X termination mix, 0.02 μL of DNA polymerase (Sequenom) and between 600–1,200 nM of the extension primers was used in both the initial (denaturation at 94°C for 30 sec, followed by 5 annealing and extension cycles at 52 and 80°C, respectively) and secondary (40 cycles of: 5-sec denaturation at 94°C, 5-sec annealing at 52°C and 5-sec extension at 80°C) iPLEX reactions. A final extension step (3 min at 72°C) was conducted prior to cooling at 20°C. Products were diluted and desalted with 15 μL sterile water and 3 μL of resin prior to spotting onto a SpectroChip (Sequenom) for analysis in the Compact Mass Spectrometer, using the MassARRAY Workstation software version 3.3 (Sequenom). Genotype accuracy was calculated for all SNPs tested at 99.95%.

Statistical analyses

We calculated HWE, allele frequencies and assessed LD using the linkage disequilibrium analyzer software (Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences and Peking Union Medical College, National Laboratory of Medical Molecular Biology, Beijing, People's Republic of China).

To estimate the relative risk of cancer associated with each SNP, we calculated the odds ratio (OR) and 95% confidence interval (95% CI) using multivariable logistic regression in SAS version 9.1 (SAS Institute, Cary, NC). Initial models adjusted only for age and sex; final models included terms for age, sex, BMI ($<$25 kg/m^2, 25–29.9 kg/m^2, $>$30 kg/m^2), cumulative smoking history (never smokers, 1–29 pack-years, 30+ pack-years), mean alcohol consumption (never drinkers, 1–6 drinks/week, 7+ drinks/week) and frequency of esophago-gastric reflux symptoms 10 years prior to diagnosis (never, less than weekly, weekly or more often).

We assessed biologic interaction by creating new variables that reclassified participants according to their genotype and frequency of gastroesophageal reflux, and separately, cumulative smoking history. Risks for each category of combined genotype-environmental exposure were estimated relative to the reference category (*i.e.*, consensus genotype and either infrequent (less than weekly) symptoms of reflux or never smoker, respectively) in multivariable logistic regression analyses. To quantify biological interaction, we calculated the synergy index S[29] and 95% confidence intervals using the algorithm of Andersson *et al.*[30] The synergy index is the ratio of the excess risk among those exposed to both factors jointly to the sum of the excess risks for exposure to each factor alone and is calculated as follows:

$$S = \frac{[\mathrm{OR}(\mathrm{AB}) - 1]}{[\mathrm{OR}(\mathrm{A}\overline{\mathrm{B}}) + \mathrm{OR}(\overline{\mathrm{A}}\mathrm{B}) - 2]},$$

where $\mathrm{OR}(\mathrm{A}\overline{\mathrm{B}})$ is the odds ratio for those exposed to A but not B, and $\mathrm{OR}(\overline{\mathrm{A}}\mathrm{B})$ is the odds ratio for those exposed to B but not A. A synergy index of 1.0 indicates no interaction, whereas an index of 3.0, for example, indicates that the risk of disease in those exposed to both factors is 3 times greater than expected if the 2 factors were completely independent.

Results

Complete epidemiologic data were available for 367 and 426 case patients with EAC and EGJAC, respectively (data from 310 patients with squamous cell carcinomas of the esophagus were not included in these analyses). Of these, blood samples were available for 263 (72%) EAC patients and 303 (70%) EGJAC patients. Within each of the case groups, there were no differences in age, sex, smoking, alcohol or history of gastroesophageal reflux between those for whom blood samples were and were not available. However, eligible controls who did not provide a blood sample (n = 187, 15%) were younger (56.0 vs 61.1 years, $p < 0.01$) and more likely to be female (41% vs 33%, $p = 0.03$) than controls who provided a blood sample (n = 1,393; 85%), and were also less likely to report frequent reflux symptoms or overweight/obesity. As expected, the prevalences of smoking, high body mass and gastroesophageal reflux were all significantly higher among EAC and EGJAC cases than population controls (Table I).

MGMT *polymorphisms and risks of cancer*

Minor allele frequencies and genotype frequencies for each of the SNPs are presented in Table II. As the *MGMT* SNPs I143V (rs2308321) and K178R (rs2308327) were in complete LD, we have presented results only for I143V. There were no deviations from HWE for any of the SNPs.

For 3 of the *MGMT* polymorphisms examined (rs12269324, rs12268840 and I143V), we observed significantly higher frequencies of the minor allele among EAC cases than controls (Table II). At the genotype level, carriers of homozygous variant genotypes were found to have 60–100% higher risks of EAC than those with consensus genotypes. Multivariate adjustment for smoking, alcohol consumption, BMI and gastro-esophageal reflux made essentially no difference to the risk estimates. Highest risks were associated with homozygous *MGMT* rs12268840 carriers (OR 2.0, 95% CI 1.3–3.2), for which there was a significant trend of increasing risk per allele ($p_{\mathrm{trend}} = 0.002$). Smaller and less consistent associations were observed between the *MGMT* SNPs and EGJAC.

DNA repair gene polymorphisms and risks of cancer

The frequency of the minor allele of *ERCC1* N118N (rs11615) was significantly lower among EAC and EGJAC cases than controls. Homozygous carriers of synonymous variant *ERCC1* N118N had lower risks of EAC and EGJAC than wild-type, although risk estimates were attenuated to borderline statistical significance after adjusting for potentially confounding factors. There was no evidence that *XPD* polymorphism K751Q (rs13181) was associated with either EAC or EGJAC (Table II). *XRCC1* Q399R (rs25487) was associated with significantly increased risks of EGJAC per allele ($p = 0.04$), and homozygous carriers were at increased risk compared to wild-type (OR 1.6, 95% CI 1.1–2.4). While the magnitude of risk estimates associated with various genotypes appeared to vary between EAC and EGJAC, we found no statistical evidence of heterogeneity between these 2 sites for any of the genotypes (data not shown).

Assessment of interaction of genotypes with gastro-esophageal reflux

We reclassified participants into combined exposure categories according to their genotype status and frequency of gastroesophageal reflux symptoms and cumulative smoking exposure. Among those who reported reflux symptoms less than weekly, we observed modest, nonsignificant increases in risks of EAC associated with variant *MGMT* genotypes compared to the reference category (Table III). Relative risks of EAC were substantially higher among those who reported reflux symptoms weekly or more often. For 2 *MGMT* loci (rs12269324 and rs12268840), we found evidence of biological interactions whereby homozygous variant genotype carriers with reflux symptoms weekly or more often had markedly elevated risks of EAC (rs12269324 OR 12.3, 95% CI 4.3–35; rs12268840 OR 15.5, 95% CI 5.8–42) compared to the reference category. The synergy indices for both terms suggested that the risk estimates were substantially higher than expected under simple biological additivity (rs12269324 S = 3.1, 95% CI 0.9–10; rs12268840 S = 3.3, 95% CI 1.1–10). Similar patterns were observed for EGJAC, although risks were generally of lower magnitude.

TABLE I – CHARACTERISTICS OF STUDY PARTICIPANTS WHO PROVIDED QUESTIONNAIRE DATA AND BLOOD

	Control		EAC		EGJAC	
	Frequency	%	Frequency	%	Frequency	%
N	1337		263		303	
Age (years)						
mean (±SD)	61 (12)		63 (10)		65 (9)	
Gender						
Female	449	34	23	9	39	13
Male	888	66	240	91	264	87
Ethnicity						
Caucasian	1283	96	261	99	300	99
Asian	25	2	1	0	1	0
Other	28	2	–	–	1	0
Missing	1	0	1	0	1	0
p-value			0.2		0.01	
Education						
No further study	541	40	121	46	124	41
Trade	598	45	124	47	145	48
Tertiary	196	15	17	7	33	1
Missing	2	0	1	0	1	0
p-value			0.002		0.2	
Income (AUD)						
Less than 30,000	493	37	128	49	126	41
30,000–60,000	369	28	56	21	84	28
Over 60,000	366	28	55	21	66	22
Missing	109	7	24	9	27	9
p-value			<0.001		0.1	
BMI (kg/m^2)						
<25	465	35	44	17	74	24
25–29.9	569	43	110	42	125	41
30+	277	21	99	38	95	31
Missing	26	1	10	3	9	4
p-value			<0.001		<0.001	
Smoking (pack-years)						
Never smoker	600	45	64	24	76	25
1–29	510	38	107	41	124	41
30+	227	17	92	35	103	34
p-value			<0.001		<0.001	
Alcohol (drinks/week)						
Never-drinker	175	13	24	9	31	10
1–6	468	35	61	23	85	28
7+	694	52	177	67	187	62
Missing	0	0	1	0	0	0
p-value			<0.001		0.008	
Heartburn/acid reflux						
Never	575	43	56	21	82	27
<weekly	590	44	95	36	112	37
≥weekly	171	13	110	42	108	36
Missing	1	0	2	0	1	0
p-value			<0.001		<0.001	

NB: some % columns do not add to 100 from rounding.

We found no evidence of biological interactions with gastroesophageal reflux for *XPD* K751Q (rs13181) or *XRCC1* Q399R (rs25487). Risks associated with *ERCC1* N118N genotypes exhibited a heterogeneous pattern when combined with reflux symptoms. Among those with reflux symptoms less than weekly, variant *ERCC1* N118N alleles were associated with significantly lower risks of esophageal adenocarcinoma. Among those with reflux symptoms weekly or more often, the risks increased from 3.5 (95% CI 2.1–5.9) for those with consensus genotype to 5.0 (95% CI 2.4–11) for those with homozygous variant alleles.

Assessment of interaction of genotypes with cumulative smoking history

After reclassifying participants according to their smoking history and *MGMT* SNP genotype status, we found that for each genotype except homozygous variant *MGMT* I143V, there were stepwise increases in risk of EAC and EGJAC with increasing levels of smoking (Table IV). For the 2 intronic SNPs (rs12269324, rs12268840), variant homozygotes who were heavy smokers had substantially higher risks of EAC (rs12269324 OR 3.7, 95%CI 1.4–10.1; rs12268840 OR 5.3, 95% CI 2.1–13.3) than wild-type heavy smokers or homozygous never smokers. Although the synergy indices for these associations were consistent with greater than additive interaction, they failed to reach statistical significance.

There was no evidence that the combined presence of variant genotypes of *ERCC1* N118N, *XPD* K751Q or *XRCC1* Q399R and large cumulative exposures to smoking conferred risks of EAC or EGJAC that differed from expectation under an additive model (Table IV).

Discussion

In this large, population-based study, we found statistically significant associations between polymorphisms in the *MGMT* gene and risks of EAC, and to a lesser extent, EGJAC. Our data suggest that risks associated with these polymorphisms are significantly higher among people with frequent symptoms of gastroesophageal reflux than people with infrequent symptoms and perhaps among heavy smokers. The few previous investigations of genes encoding DNA repair proteins and risk of EAC have yielded inconsistent findings. A Canadian study of 56 EAC patients reported significantly lower risks for EAC for *XPD* K751Q homozygotes (OR 0.24, 95% CI 0.07–0.88),[21] whereas a Swedish case-control study reported significantly increased risks for the same polymorphism (OR 2.7, 95%CI 1.3–5.9).[22] Most recently, a hospital-based case-control study reported modestly increased risks of EAC among *XPD* K751Q homozygotes compared to consensus (OR 1.73, 95%CI 0.94–3.15).[23] Our null finding lies in the middle of these widely dispersed estimates, and thus we cannot exclude chance as an explanation for these findings.

We found no evidence that *XRCC1* Q399R was associated with risk of EAC, an observation similar to those reported by the Canadian,[21] Swedish[22] and US studies.[23] We did however, observe a modestly increased risk of EGJAC associated with this polymorphism.

Of the loci tested, only *ERCC1* N118N was associated with lower risks than consensus for both EAC and EGJAC, an association that was strongest for those patients who were never smokers. Similar inverse associations between *ERCC1* polymorphisms and risk of lung cancer have been reported,[31,32] although we are not aware of any previous reports for EAC. Furthermore, although a recent meta-analysis showed no association between this locus and lung cancer,[33] 2 other studies[34,35] have reported a smoking mediated effect of *ERCC1* on lung cancer risk. Interestingly, our study shows that an original significant increase in risk of EAC is present for ≥30 smoking pack years is reduced considerably for *ERCC1* homozygotes. Hence we hypothesize that this smoking-ERCC1 genotype mediation effect is also present for esophageal adenocarcinoma.

Strengths of the present study include the population-based sampling frame for cases and controls, the large size of the sample and the comprehensive collection of data with which to control potential confounding and explore biologic interactions. A potential weakness of the study was the low participation rate among cases and controls, raising concerns about possibly biased selection of participants. The principal reason for nonparticipation among potential cases was ill health or death, an acknowledged difficulty in studies investigating rapidly fatal conditions. Although the age and sex distributions of the participating cases were similar to the distribution of all potentially eligible cases notified to the Australian National Cancer Statistics Clearing House (2002), we were unable to obtain further details describing the characteristics of nonparticipating cases due to privacy laws. Bias might arise if the genotypes of interest were correlated with survival from esophageal cancer. For example, if esophageal cancer patients with consensus *MGMT* genotypes had poorer survival than those with variant *MGMT* genotypes, then case-control stud-

TABLE II – ASSOCIATIONS BETWEEN POLYMORPHISMS IN MULTIPLE DNA REPAIRS GENES AND EAC AND EJGAC

Locus	Control		EAC				EGJAC			
	Genotype	Proportion	Proportion	*p*-value	OR[1] (95% CI)	OR[2] (95% CI)	Proportion	*p*-value	OR[1] (95% CI)	OR[2] (95% CI)
MGMT	TT	0.58	0.50		1.0 (ref)	1.0 (ref)	0.53		1.0 (ref)	1.0 (ref)
rs12269324	TA	0.34	0.40		1.3 (1.0–1.7)	1.4 (1.0–1.9)	0.41		1.3 (1.0–1.8)	1.3 (1.0–1.8)
	AA	0.08	0.10		1.4 (0.9–2.2)	1.6 (1.0–2.8)	0.06		0.9 (0.5–1.7)	1.0 (0.6–1.8)
	Minor allele	0.25	0.30	0.02		$p_{trend} = 0.02$	0.27	0.4		$p_{trend} = 0.26$
MGMT	CC	0.53	0.44		1.0 (ref)	1.0 (ref)	0.49		1.0 (ref)	1.0 (ref)
rs12268840	CT	0.37	0.42		1.3 (1.0–1.8)	1.4 (1.0–1.9)	0.40		1.2 (0.9–1.6)	1.2 (0.9–1.6)
	TT	0.10	0.14		1.7 (1.1–2.6)	2.0 (1.3–3.2)	0.11		1.2 (0.8–1.8)	1.4 (0.9–2.2)
	Minor allele	0.28	0.35	0.005		$p_{trend} = 0.002$	0.31	0.3		$p_{trend} = 0.13$
MGMT L84F	CC	0.77	0.73		1.0 (ref)	1.0 (ref)	0.74		1.0 (ref)	1.0 (ref)
rs12917	CT	0.21	0.25		1.3 (1.0–1.8)	1.5 (1.0–2.1)	0.23		1.1 (0.8–1.6)	1.1 (0.8–1.5)
	TT	0.02	0.02		1.4 (0.6–3.5)	1.5 (0.5–3.9)	0.03		1.5 (0.7–3.4)	1.5 (0.6–3.5)
	Minor allele	0.12	0.15	0.1		$p_{trend} = 0.05$	0.14	0.3		$p_{trend} = 0.34$
MGMT I143V	AA	0.75	0.66		1.0 (ref)	1.0 (ref)	0.75		1.0 (ref)	1.0 (ref)
rs2308321	AG	0.23	0.30		1.4 (1.1–1.9)	1.2 (0.9–1.7)	0.23		1.0 (0.8–1.4)	1.0 (0.7–1.4)
	GG	0.02	0.04		1.9 (0.9–3.9)	2.0 (0.9–4.4)	0.02		0.9 (0.4–2.2)	0.8 (0.3–2.0)
	Minor allele	0.13	0.19	<0.001		$p_{trend} = 0.08$	0.14	0.7		$p_{trend} = 0.76$
ERCC1 N118N	TT	0.36	0.42		1.0 (ref)	1.0 (ref)	0.45		1.0 (ref)	1.0 (ref)
rs11615	TC	0.49	0.46		0.8 (0.6–1.0)	0.8 (0.6–1.1)	0.44		0.7 (0.5–0.9)	0.7 (0.6–1.0)
	CC	0.15	0.12		0.7 (0.4–1.0)	0.6 (0.4–1.1)	0.11		0.7 (0.4–1.0)	0.7 (0.4–1.1)
	Minor allele	0.39	0.35	0.06		$p_{trend} = 0.06$	0.33	0.007		$p_{trend} = 0.03$
XPD K751Q	AA	0.43	0.41		1.0 (ref)	1.0 (ref)	0.42		1.0 (ref)	1.0 (ref)
rs13181	AC	0.44	0.47		1.2 (0.9–1.6)	1.2 (0.9–1.6)	0.46		1.1 (0.9–1.5)	1.1 (0.9–1.5)
	CC	0.13	0.12		1.0 (0.6–1.5)	0.9 (0.6–1.5)	0.12		1.0 (0.7–1.6)	1.1 (0.7–1.6)
	Minor allele	0.35	0.35	0.9		$p_{trend} = 0.74$	0.35	0.9		$p_{trend} = 0.60$
XRCC1 Q399R	AA	0.41	0.43		1.0 (ref)	1.0 (ref)	0.38		1.0 (ref)	1.0 (ref)
rs25487	AG	0.47	0.44		0.9 (0.7–1.2)	1.0 (0.7–1.3)	0.46		1.0 (0.8–1.4)	1.2 (0.9–1.6)
	GG	0.12	0.13		1.1 (0.7–1.7)	1.0 (0.6–1.6)	0.16		1.4 (0.9–2.0)	1.6 (1.1–2.4)
	Minor allele	0.36	0.35	0.8		$p_{trend} = 0.75$	0.39	0.1		$p_{trend} = 0.04$

[1]Odds ratio and 95% confidence interval adjusted for age (in years) and sex only.–[2]Odds ratio and 95% confidence interval adjusted for age (in years), sex, BMI, cumulative smoking history, mean alcohol consumption and frequency of gastroesophageal reflux symptoms 10 years prior to diagnosis.

TABLE III – JOINT EFFECTS OF GENOTYPE AND ACID REFLUX/HEARTBURN ON THE RISK OF EAC AND EGJAC

Locus	Genotype	EAC		EGJAC	
		Frequency of reflux symptoms		Frequency of reflux symptoms	
		<weekly	≥weekly	<weekly	≥weekly
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
MGMT	TT	1.0 (ref)	4.4 (2.8–6.7)	1.0 (ref)	3.4 (2.3–5.1)
rs12269324	TA	1.4 (1.0–2.0)	5.3 (3.2–8.9)	1.4 (1.0–1.9)	4.3 (2.7–7.0)
	AA	1.3 (0.7–2.5)	12.3 (4.3–35)	0.7 (0.4–1.4)	7.9 (2.6–24)
S (95%CI)			3.1 (0.9–10)		3.3 (0.8–13)
MGMT	CC	1.0 (ref)	4.6 (2.9–7.4)	1.0 (ref)	3.5 (2.3–5.4)
rs12268840	CT	1.5 (1.0–2.1)	5.5 (3.4–9.2)	1.2 (0.9–1.7)	3.8 (2.4–6.1)
	TT	1.7 (1.0–3.0)	15.5 (5.8–42)	1.2 (0.7–2.0)	8.5 (3–24)
S (95%CI)			3.3 (1.1–10)		2.8 (0.8–9.7)
MGMT L84F	CC	1.0 (ref)	5.2 (3.6–7.5)	1.0 (ref)	3.3 (2.3–4.7)
rs12917	CT	1.7 (1.1–2.6)	4.4 (2.4–8.2)	1.0 (0.7–1.5)	4.6 (2.6–7.9)
	TT	1.7 (0.6–5.3)	5.9 (0.8–46)	1.5 (0.6–4.0)	4.7 (0.6–35)
S (95%CI)			1.0 (0.1–12)		1.3 (0.1–18)
MGMT I143V	AA	1.0 (ref)	3.8 (2.5–5.5)	1.0 (ref)	3.8 (2.6–5.3)
rs2308321	AG	0.9 (0.6–1.4)	6.7 (4.0–11)	1.1 (0.7–1.5)	3.1 (1.7–5.5)
	GG	2.6 (1.1–6.0)	2.3 (0.4–13)	0.9 (0.3–2.7)	2.2 (0.4–12)
S (95%CI)			0.3 (0.01–6.7)		0.5 (0.02–10)
ERCC1 N118N	TT	1.0 (ref)	3.5 (2.1–5.9)	1.0 (ref)	4.5 (2.8–7.1)
rs11615	TC	0.8 (0.5–1.1)	3.1 (1.9–4.9)	0.8 (0.6–1.1)	2.3 (1.4–3.6)
	CC	0.4 (0.2–0.8)	5.0 (2.4–11)	0.7 (0.4–1.2)	2.5 (1.1–5.6)
S (95%CI)			2.1 (0.6–7.1)		0.7 (0.04–10)
XPD K751Q	AA	1.0 (ref)	3.5 (2.1–5.8)	1.0 (ref)	3.2 (2.0–5.1)
rs13181	AC	1.1 (0.8–1.6)	5.3 (3.3–8.6)	1.1 (0.8–1.5)	4.3 (2.7–6.8)
	CC	0.8 (0.4–1.5)	4.5 (2.1–9.7)	1.1 (0.6–1.8)	3.2 (1.5–6.9)
S (95%CI)			1.5 (0.5–4.8)		1.0 (0.3–3.3)
XRCC1 Q399R	AA	1.0 (ref)	3.2 (2.0–5.3)	1.0 (ref)	4.1 (2.6–6.6)
rs25487	AG	0.7 (0.5–1.1)	4.5 (2.8–7.2)	1.3 (0.9–1.8)	3.9 (2.4–6.4)
	GG	1.0 (0.6–1.7)	3.6 (1.6–8.2)	1.6 (1.0–2.6)	6.0 (2.8–13)
S (95%CI)			1.2 (0.3–4.2)		1.3 (0.5–3.5)

Odds ratio and 95% confidence interval adjusted for age (in years), sex, BMI, cumulative smoking history, mean alcohol consumption and frequency of gastroesophageal reflux symptoms 10 years prior to diagnosis. S, synergy index and 95% confidence interval.

TABLE IV – JOINT EFFECTS OF GENOTYPE AND CIGARETTE SMOKING ON THE RISK OF EAC AND EGJAC

Locus	Genotype	EAC			EGJAC		
		Never smoker	1–30 pack-years	≥30 pack-years	Never smoker	1–30 pack-years	≥30 pack-years
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
MGMT	TT	1.0 (ref)	1.5 (0.9–2.5)	2.2 (1.3–4.0)	1.0 (ref)	1.5 (1.0–2.4)	2.1 (1.3–3.5)
rs12269324	TA	1.4 (0.8–2.5)	2.0 (1.1–3.4)	3.2 (1.7–5.9)	1.1 (0.6–1.8)	2.1 (1.3–3.4)	3.5 (2.0–6.2)
	AA	1.2 (0.4–3.7)	2.8 (1.3–6.2)	3.7 (1.4–10.1)	0.8 (0.3–2.4)	1.7 (0.7–3.8)	2.1 (0.7–5.7)
S (95%CI)				1.9 (0.36–10)			1.2 (0.1–11)
MGMT	CC	1.0 (ref)	1.4 (0.8–2.4)	2.1 (1.2–3.8)	1.0 (ref)	1.6 (1.0–2.5)	2.1 (1.3–3.6)
rs12268840	CT	1.4 (0.8–2.5)	2.0 (1.1–3.4)	2.9 (1.6–5.5)	1.0 (0.6–1.7)	1.9 (1.1–3.0)	2.9 (1.6–5.0)
	TT	1.5 (0.6–4.0)	2.9 (1.4–6.1)	5.3 (2.1–13.3)	1.2 (0.5–2.9)	2.0 (1.0–4.2)	3.4 (1.5–8.1)
S (95%CI)				2.7 (0.6–11)			1.8 (0.4–8.1)
MGMT L84F	CC	1.0 (ref)	1.5 (1.0–2.3)	2.5 (1.5–4.0)	1.0 (ref)	1.7 (1.1–2.5)	2.9 (1.9–4.5)
rs12917	CT	1.7 (0.9–3.1)	2.4 (1.4–4.3)	2.5 (1.3–4.9)	1.5 (0.8–2.6)	2.3 (1.3–3.9)	1.7 (0.9–3.3)
	TT	1.6 (0.2–13.0)	1.8 (0.5–7.5)	5.4 (0.6–48.7)	0.9 (0.1–7.4)	2.7 (0.8–9.0)	6.2 (0.9–41.6)
S (95%CI)				2.1 (0.1–49)			2.8 (0.2–35)
MGMT I143V	AA	1.0 (ref)	1.5 (0.9–2.3)	2.5 (1.5–4.1)	1.0 (ref)	1.7 (1.1–2.5)	2.8 (1.8–4.3)
rs2308321	AG	1.2 (0.6–2.3)	2.3 (1.3–3.9)	2.1 (1.1–3.9)	1.1 (0.6–2.0)	2.0 (1.2–3.4)	1.9 (1.0–3.5)
	GG	6.4 (1.5–27.6)	0.9 (0.2–4.5)	5.8 (1.7–20.2)	1.2 (0.1–11.5)	1.2 (0.3–4.7)	2.0 (0.4–10.0)
S (95%CI)				0.7 (0.1–5.0)			0.5 (0.02–16)
ERCC1 N118N	TT	1.0 (ref)	1.2 (0.7–2.2)	2.2 (1.2–4.0)	1.0 (ref)	2.5 (1.5–4.2)	3.2 (1.8–5.7)
rs11615	TC	0.8 (0.4–1.4)	1.1 (0.6–1.9)	1.6 (0.9–2.9)	1.0 (0.6–1.7)	1.4 (0.8–2.4)	2.3 (1.3–4.2)
	CC	0.3 (0.1–0.9)	1.3 (0.6–2.7)	1.2 (0.5–3.0)	1.4 (0.7–3.0)	1.1 (0.5–2.4)	1.8 (0.8–4.4)
S (95%CI)				0.5 (0.0–71)			0.3 (0.1–1.9)
XPD K751Q	AA	1.0 (ref)	1.2 (0.7–2.0)	1.9 (1.0–3.5)	1.0 (ref)	1.8 (1.1–3.0)	2.0 (1.1–3.5)
rs13181	AC	0.8 (0.4–1.5)	1.6 (1.0–2.8)	2.6 (1.4–4.7)	1.0 (0.6–1.7)	1.7 (1.0–2.8)	3.3 (1.9–5.8)
	CC	1.1 (0.5–2.3)	1.2 (0.6–2.8)	1.1 (0.4–3.2)	1.3 (0.6–2.6)	1.7 (0.8–3.5)	1.8 (0.7–4.4)
S (95%CI)				0.1 (0.0–4906)			0.6 (0.1–4.7)
XRCC1 Q399R	AA	1.0 (ref)	2.6 (1.5–4.7)	2.9 (1.5–5.5)	1.0 (ref)	2.1 (1.2–3.7)	2.7 (1.5–4.9)
rs25487	AG	1.5 (0.8–2.8)	1.5 (0.8–2.7)	2.9 (1.5–5.4)	1.4 (0.8–2.4)	2.1 (1.2–3.6)	3.4 (1.9–6.0)
	GG	1.6 (0.7–3.7)	1.8 (0.8–4.0)	3.4 (1.4–8.3)	2.0 (1.0–4.1)	2.7 (1.4–5.4)	4.2 (1.9–9.4)
S (95%CI)				1.0 (0.3–3.6)			1.2 (0.4–3.5)

Odds ratio and 95% confidence interval adjusted for age (in years), sex, BMI, cumulative smoking history, mean alcohol consumption and frequency of gastroesophageal reflux symptoms 10 years prior to diagnosis. *S*, synergy index and 95% confidence interval.

ies of surviving cases would observe spurious risk associations with variant *MGMT*. Although such bias is possible, we consider this an unlikely explanation for the observed interactions with reflux. The *MGMT* SNP frequencies in our control series were similar to those reported by others,[15] hence biased sampling with respect to genotype among controls is unlikely.

Our findings suggest that 2 loci within *MGMT* (rs12268840 and I143V) are of interest for esophageal adenocarcinoma. If we were to adjust for multiple comparisons using the Bonferroni adjustment, we would need to compare our *p*-values to an adjusted alpha of 0.007 (0.05/7; 7 SNPs tested). Our results (rs12268840: $p = 0.005$ and I143V: $p = 0.0007$) fall below this specified cut off point. Many would argue that this is the correct adjustment, although there is a counterargument that this correction is not appropriate and overly conservative.[36]

Assuming that our findings are not the result of error, then the question arises as to how *MGMT* polymorphisms might influence risk of EAC and EGJAC. *MGMT* is a candidate gene of increasing interest with respect to EAC and EGJAC, since the 2 strongest risk factors, gastroesophageal reflux and smoking, are mutagenic through DNA alkylation. Our finding that the risks of EAC in particular were significantly higher among those with the common *MGMT* variants than those with consensus *MGMT* sequence suggests that this gene plays a role in modulating susceptibility. Moreover, the observation that the combined risks associated with *MGMT* variants and frequent episodes of gastroesophageal reflux were greater than the sum of either factor in isolation is strong evidence for a biological interaction, as might be expected if reflux acts through a pathway of nitrosation of salivary nitrites.[7,8] However, such explanations must take into account the relatively small genotype-environment category sizes, and as such a reduced power to reflect real population inferences.

We have shown a large increase in risk of EAC from the combination of an intronic SNP (rs12268840) in MGMT and gastroesophageal reflux. Many have postulated that causative genetic variants must involve nonsynonymous coding region mutations, leading to changes in the configuration of the protein and hence changes in function. The *MGMT SNP* that we have identified as conferring highest risk of adenocarcinoma was intronic, however the variant T allele leads to a new binding site for a transcription factor, namely AML1a. [Acute Myeloid Leukemia 1a]. This transcription factor is a site-specific DNA-binding protein that plays a role in leukemia development, however its role in DNA repair remains unclear. We cautiously speculate that this factor might also play a role in the development of at least some EAC.

In conclusion, we have identified an increased risk of esophageal adenocarcinoma among those with polymorphisms in *MGMT*, particularly the intronic SNP rs12268840. We have also shown that the risks associated with this polymorphism appear to be greatly increased among people with frequent episodes of gastroesophageal reflux, and possibly with smoking. Although our findings point to a strong gene-by-environment interaction with rs12268840, we cannot exclude the possibility that this SNP is in LD with causal variants in *MGMT*. The risks associated with other DNA repair genes were small and inconsistent. Further insights into possible causal mechanisms for *MGMT* with respect to esophageal adenocarcinoma may be gained from laboratory and animal investigations.

Acknowledgements

The funding bodies played no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript. We are grateful to Dr. Harish Babu for assisting with pathology abstractions. We wish to thank all of the study participants.

References

1. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF, Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. JAMA 1991;265:1287–9.
2. Lord RV, Law MG, Ward RL, Giles GG, Thomas RJ, Thursfield V. Rising incidence of oesophageal adenocarcinoma in men in Australia. J Gastroenterol Hepatol 1998;13:356–62.
3. Wayman J, Forman D, Griffin SM. Monitoring the changing pattern of esophago-gastric cancer: data from a UK regional cancer registry. Cancer Causes Control 2001;12:943–9.
4. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 2005;97:142–6.
5. Chow WH, Finkle WD, McLaughlin JK, Frankl H, Ziel HK, Fraumeni JF, Jr. The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. JAMA 1995;274:474–7.
6. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340:825–31.
7. McColl KE. When saliva meets acid: chemical warfare at the oesophagogastric junction. Gut 2005;54:1–3.
8. Suzuki H, Iijima K, Scobie G, Fyfe V, McColl KE. Nitrate and nitrosative chemistry within Barrett's oesophagus during acid reflux. Gut 2005;54:1527–35.
9. Iijima K, Henry E, Moriya A, Wirz A, Kelman AW, McColl KE. Dietary nitrate generates potentially mutagenic concentrations of nitric oxide at the gastroesophageal junction. Gastroenterology 2002;122:1248–57.
10. Suzuki H, Iijima K, Moriya A, McElroy K, Scobie G, Fyfe V, McColl KE. Conditions for acid catalysed luminal nitrosation are maximal at the gastric cardia. Gut 2003;52:1095–101.
11. Felley-Bosco E. Role of nitric oxide in genotoxicity: implication for carcinogenesis. Cancer Metastasis Rev 1998;17:25–37.
12. Hecht SS. DNA adduct formation from tobacco-specific N-nitrosamines. Mutat Res 1999;424:127–42.
13. Schuller HM. Mechanisms of smoking-related lung and pancreatic adenocarcinoma development. Nat Rev Cancer 2002;2:455–63.
14. Kaina B, Christmann M, Naumann S, Roos WP. MGMT: key node in the battle against genotoxicity, carcinogenicity and apoptosis induced by alkylating agents. DNA Repair (Amst) 2007;6:1079–99.
15. Pegg AE, Fang Q, Loktionova NA. Human variants of O6-alkylguanine-DNA alkyltransferase. DNA Repair (Amst) 2007;6:1071–8.
16. Margison GP, Heighway J, Pearson S, McGown G, Thorncroft MR, Watson AJ, Harrison KL, Lewis SJ, Rohde K, Barber PV, O'Donnell P, Povey AC, et al. Quantitative trait locus analysis reveals two intragenic sites that influence O6-alkylguanine-DNA alkyltransferase activity in peripheral blood mononuclear cells. Carcinogenesis 2005;26:1473–80.
17. Wang L, Zhu D, Zhang C, Mao X, Wang G, Mitra S, Li BF, Wang X, Wu M. Mutations of O6-methylguanine-DNA methyltransferase gene in esophageal cancer tissues from Northern China. Int J Cancer 1997;71:719–23.
18. Wang L, Liu H, Zhang Z, Spitz MR, Wei Q. Association of genetic variants of O6-methylguanine-DNA methyltransferase with risk of lung cancer in non-Hispanic Whites. Cancer Epidemiol Biomarkers Prev 2006;15:2364–9.
19. Egyhazi S, Ma S, Smoczynski K, Hansson J, Platz A, Ringborg U. Novel O6-methylguanine-DNA methyltransferase SNPs: a frequency comparison of patients with familial melanoma and healthy individuals in Sweden. Hum Mutat 2002;20:408–9.
20. Hall J, Hashibe M, Boffetta P, Gaborieau V, Moullan N, Chabrier A, Zaridze D, Shangina O, Szeszenia-Dabrowska N, Mates D, Janout V, Fabianova E, et al. The association of sequence variants in DNA repair and cell cycle genes with cancers of the upper aerodigestive tract. Carcinogenesis 2007;28:665–71.
21. Casson AG, Zheng Z, Evans SC, Veugelers PJ, Porter GA, Guernsey DL. Polymorphisms in DNA repair genes in the molecular pathogenesis of esophageal (Barrett) adenocarcinoma. Carcinogenesis 2005;26:1536–41.
22. Ye W, Kumar R, Bacova G, Lagergren J, Hemminki K, Nyren O. The XPD 751Gln allele is associated with an increased risk for esophageal adenocarcinoma: a population-based case-control study in Sweden. Carcinogenesis 2006;27:1835–41.
23. Liu G, Zhou W, Yeap BY, Su L, Wain JC, Poneros JM, Nishioka NS, Lynch TJ, Christiani DC. XRCC1 and XPD polymorphisms and esophageal adenocarcinoma risk. Carcinogenesis 2007;28:1254–8.
24. Whiteman DC, Sadeghi S, Pandeya N, Smithers BM, Gotley DC, Bain CJ, Webb PM, Green AC for the Australian Cancer Study. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. Gut 2008;57:173–80.
25. Spechler SJ, Dixon MF, Genta R, Hainaut P, Lambert R, Siewert R. Adenocarcinoma of the oesophago-gastric junction. In: Hamilton SR, Aaltonen LA. Pathology and genetics. Tumours of the digestive system. WHO classification of tumours, 2nd edn. Lyon: IARC Press, 2000.
26. Jordan SJ, Green AC, Whiteman DC, Webb PM. Risk factors for benign serous and mucinous epithelial ovarian tumors. Obstet Gynecol 2007;109:647–54.
27. Murray L, Johnston B, Lane A, Harvey I, Donovan J, Nair P, Harvey R. Relationship between body mass and gastro-oesophageal reflux symptoms: the bristol helicobacter project. Int J Epidemiol 2003;32:645–50.
28. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. Ann Intern Med 2005;143:199–211.
29. Rothman KJ. Modern epidemiology, 1st edn. Boston: Little, Brown and Co., 1986.
30. Andersson T, Alfredsson L, Kallberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. Eur J Epidemiol 2005;20:575–9.
31. Kiyohara C, Yoshimasu K. Genetic polymorphisms in the nucleotide excision repair pathway and lung cancer risk: a meta-analysis. Int J Med Sci 2007;4:59–71.
32. Zienolddiny S, Campa D, Lind H, Ryberg D, Skaug V, Stangeland L, Phillips DH, Canzian F, Haugen A. Polymorphisms of DNA repair genes and risk of non-small cell lung cancer. Carcinogenesis 2006;27:560–7.
33. Li Y, Gu S, Wu Q, Li Y, Fu X, Mao Y, Huang Y, Xie Y. No association of ERCC1 C8092A and T19007C polymorphisms to cancer risk: a meta-analysis. Eur J Hum Genet 2007;15:967–73.
34. Zhou W, Liu G, Park S, Wang Z, Wain JC, Lynch TJ, Su L, Christiani DC. Gene-smoking interaction associations for the ERCC1 polymorphisms in the risk of lung cancer. Cancer Epidemiol Biomarkers Prev 2005;14:491–6.
35. Park SY, Hong YC, Kim JH, Kwak SM, Cho JH, Lee HL, Ryu JS. Effect of ERCC1 polymorphisms and the modification by smoking on the survival of non-small cell lung cancer patients. Med Oncol 2006;23:489–98.
36. Thomas DC, Clayton DG. Betting odds and genetic associations. J Natl Cancer Inst 2004;96:421–3.

GASTROENTEROLOGY 2010;139:73–83

CLINICAL—ALIMENTARY TRACT

Association of *Helicobacter pylori* Infection With Reduced Risk for Esophageal Cancer Is Independent of Environmental and Genetic Modifiers

DAVID C. WHITEMAN, PRIYA PARMAR, PAUL FAHEY, SUZANNE P. MOORE, MITCHELL STARK, ZHEN ZHEN ZHAO, GRANT W. MONTGOMERY, ADÈLE C. GREEN, NICHOLAS K. HAYWARD, and PENELOPE M. WEBB for the Australian Cancer Study

Queensland Institute of Medical Research, Brisbane, Australia

This article has an accompanying continuing medical education activity on page e11. Learning Objective: Upon completion of reading this article, successful learners will be able to identify the strengths and limitations of case-control studies in examining risk factors for esophageal cancer and to interpret findings of a case-control study.

See editorial on page 17.

BACKGROUND & AIMS: Infection with *Helicobacter pylori* is associated with reduced risk of esophageal adenocarcinoma (EAC), but it is not clear whether this reduction is modified by genotype, other host characteristics, or environmental factors. Furthermore, little is known about the association between *H pylori* and adenocarcinomas of the esophagogastric junction (EGJAC) or squamous cell carcinomas (ESCC). We sought to measure the association between *H pylori* infection and esophageal cancer and identify potential modifiers. **METHODS:** In an Australian, population-based, case-control study, we compared the prevalence of *H pylori* seropositivity and single nucleotide polymorphisms in interleukin (*IL*)*-1B (–31, –511)* and tumor necrosis factor (*TNF*)*-α (–308, –238)* among 260 EAC, 298 EGJAC, and 208 ESCC patients and 1346 controls. To estimate relative risks, we calculated odds ratios (OR) and 95% confidence intervals (CI) using multivariable logistic regression in the entire sample and within strata of phenotypic and genotypic risk factors. **RESULTS:** *H pylori* infection was associated with significantly reduced risks of EAC (OR, 0.45; 95% CI: 0.30–0.67) and EGJAC (OR, 0.41; 95% CI: 0.27–0.60) but not ESCC (OR, 1.04; 95% CI: 0.71–1.50). For each cancer subtype, risks were of similar magnitude across strata of reflux frequency and smoking status. We found no evidence that polymorphisms in *IL-1B* or *TNF-α* modified the association between *H pylori* and EAC or EGJAC. **CONCLUSIONS:** *H pylori* infection is inversely associated with risks of EAC and EGJAC (but not ESCC); the reduction in risk is similar across subgroups of potential modifiers.

Keywords: Esophageal Neoplasms; Case-Control Studies; Genetic and Environmental Modifiers; Acid Reflux.

Esophageal cancers are the sixth most commonly occurring cancers worldwide,[1] and their very high mortality rate accentuates their public health importance. Recent rapid rises in the incidence of adenocarcinomas of the esophagus (EAC) and esophago-gastric junction (EGJAC) and contrasting declines in the incidence of esophageal squamous cell carcinomas (ESCC) suggest population-wide changes in exposure to causal factors.[2,3] Chronic, frequent reflux of gastric acid into the distal esophagus is the primary factor underlying most cases of EAC.[4] Other factors, including obesity and smoking, have also been shown to significantly increase a person's risk of these cancers[5–10] and may act synergistically through inflammatory pathways to enhance the carcinogenic effects of gastroesophageal reflux.[11–13] On the other hand, ESCC has been most strongly associated with smoking and alcohol intake in Western populations[10,14–17] and with other environmental factors such as diet,[18,19] infections,[20] and thermal injury[21] in high-incidence populations.

Recently, attention has focused on a possible role of *Helicobacter pylori* in the changing epidemiology of EAC.[22] Infection with *H pylori* is causally associated with ulceration, atrophy, and carcinoma of the stomach and with ulceration of the duodenum. A developing body of observational data suggests that people with evidence of *H*

Abbreviations used in this paper: BMI, body mass index; CI, confidence interval; EAC, esophageal adenocarcinoma; EGJAC, esophagogastric junction adenocarcinoma; ESCC, esophageal squamous cell carcinoma; IL, interleukin; NSAIDs, nonsteroidal anti-inflammatory drugs; OR, odds ratio; PPI, proton pump inhibitors; SNP, single nucleotide polymorphism; TNF, tumor necrosis factor.

0016-5085/$36.00
doi:10.1053/j.gastro.2010.04.009

pylori infection have lower than average risks of EAC;[23] hypoacidity induced by atrophic gastritis has been proffered as one explanation for this inverse association.[22] Other physiologic *sequelae* of *H pylori* infection that also might explain the inverse association include reduced ghrelin synthesis among infected persons[24] (speculated to induce early satiety and thereby prevent obesity) and rapid gastric emptying[25] (thereby reducing the likelihood of gastroesophageal reflux).

The relationship between *H pylori* and upper gastrointestinal cancer may be more complicated than first appreciated however because it is now apparent that, for a subset of people, infection with *H pylori* leads to hyperacidity and antral predominant, nonatrophic gastritis.[26] There is evidence to suggest that infections among this group of patients may actually increase the risk of EAC.[27,28] Host cytokine responses appear to underpin these divergent clinical pathways following *H pylori* colonization, and the evidence to date most strongly implicates polymorphisms in the genes encoding interleukin (IL)-1B and tumor necrosis factor (TNA) α.[29] IL-1B is among the most potent inhibitors of gastric acid yet identified, and the T allele at the −31 locus of *IL1B* confers enhanced activity. The common *TNF-α −308A/G* (rs1800629) polymorphism is associated with an increased production of TNF-α,[30] and a recent meta-analysis concluded that the *TNF-α−308AA* genotype is associated with a moderately increased risk of gastric cancer.[31] There are grounds for predicting that another polymorphism at *TNF-α −238 A/G* (rs361525) also has functional significance,[30] although epidemiologic evidence for an association with cancers of the gastrointestinal tract is so far lacking. It has been hypothesized that the association between *H pylori* infection and the risk of adenocarcinomas of the esophagus and esophago-gastric junction is modified by polymorphisms in these proinflammatory genes that regulate gastric acid secretion. No studies to date have tested this hypothesis.

Here, we report the findings of an investigation into the association between *H pylori* infection and cancers of the esophagus conducted within a population having a low prevalence of infection (<25%). In particular, we sought to assess whether the effects of *H pylori* infection were modified by genes and other factors known or strongly suspected to be associated with risks of cancers of the esophagus.

Materials and Methods

Study Design and Participants

We used data from a nationwide case-control study of esophageal cancer conducted in Australia, the details of which have been described in full elsewhere.[13] In summary, eligible case patients were people aged 18–79 years with a histologically confirmed primary invasive cancer of the esophagus or esophago-gastric junction diagnosed between July 1, 2002 (July 1, 2001, in Queensland), and June 30, 2005, in the mainland states of Australia. Patients were recruited either through major treatment centers or state-based cancer registries. A total of 1577 patients with esophageal cancer received an invitation to participate in the study, of whom 1102 patients (858 through clinics and 244 through cancer registries) returned a completed questionnaire (70% of all invited; 35% of all living and deceased persons in mainland Australia who had been diagnosed with incident esophageal cancer). Details of the histologic type and anatomic site of each patient's tumor were abstracted from diagnostic pathology reports. All of the squamous cell carcinomas were considered "esophageal" in origin; anatomic sites of adenocarcinomas were categorized according to the World Health Organization classification into "esophageal" and "esophago-gastric junction" tumors.[32] Eight case patients were deemed ineligible on review and were excluded from the analysis. Full questionnaire data were available for 365 EAC, 426 EGJAC, and 303 ESCC patients.

Potential controls were randomly selected from the Australian Electoral Roll within strata of age (in 5-year age groups) and state of residence to match the distribution of the case series. We aimed for similar numbers of male cases and controls in each stratum of age and state; female controls were intentionally over-sampled at all ages to accommodate their simultaneous enrolment in a parallel case-control study of ovarian cancer.[33] Of 3258 potentially eligible control participants who were contacted and invited to participate, 175 were excluded (16 deceased, 61 were too ill, 98 were unable to read or write in English), and 41 were lost to follow-up shortly after initial contact. Of 3042 remaining controls, 1680 (55%) accepted the initial invitation, and 1580 returned the completed questionnaires (51% of all potentially eligible controls contacted).

Data Collection

Participants self-completed a health and lifestyle questionnaire asking about their social background and general health. We assessed the frequency of symptoms of gastroesophageal reflux 10 years before diagnosis, defined as the presence of heartburn ("a burning pain behind the breastbone after eating") or acid reflux ("a sour taste from acid or bile rising up into the mouth or throat"). For analysis, we used the highest reported frequency for either symptom and defined "frequent symptoms" as those occurring at least weekly during the 10 years before diagnosis, consistent with previous reports.[34,35] Participants were asked "Has a doctor ever told you that you have a "*Helicobacter pylori*" infection? (an infection of the lining of your stomach that can cause ulcers). (Note: this can ONLY be diagnosed by putting a

tube down your throat, or by a blood or breath test.)"; those who responded affirmatively were also asked whether they had received specific treatment for this infection. Height and weight 1 year ago (1 year before diagnosis for cases) were elicited and used to calculate the body mass index (BMI; in kg/m^2). Participants were asked whether, over their whole life, they had ever smoked more than 100 cigarettes, cigars, or pipes; positive responses elicited further questions regarding consumption and duration of smoking. We derived the number of pack-years of tobacco exposure by dividing the number of cigarettes smoked on a typical day by 20 and multiplying by the total number of years smoked. We asked participants to report the frequency with which they consumed different classes of alcohol (light beer, regular beer, white wine, red wine, port/sherry, and spirits/liqueurs) at ages 20–29, 30–49, and ≥50 years, as applicable. For these analyses, total alcohol consumption was summed across all age groups from which we calculated the average number of standard drinks (10 g ethanol) consumed per week between age 20 years and current age. We also asked participants whether they had ever used aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) during the past 5 years and, if so, the frequency of use on a 7-point scale ranging from less than once a month up to 2 or more times/per day. Finally, participants were asked whether they had every used acid-suppressant medications and were given lists of generic and trade names for H2-receptor antagonists and proton pump inhibitors (PPIs).

Blood Collection

Facilities for the systematic collection of blood became available 6 months after the study commenced, and no attempt was made to re-contact those participants who had already completed data collection. Blood samples for *H pylori* analysis and genotyping were available for 1400 controls and 269 EAC, 307 EGJAC, and 218 ESCC cases.

Serologic Methods

Following collection from study participants, serum samples were stored at −80°C and thawed immediately prior to testing. We used a commercially available, rapid enzyme-linked immunosorbent assay kit (Genesis Diagnostics Ltd, Littleport, Cambridge, UK) to detect immunoglobulin G antibodies to *H pylori* according to the manufacturer's instructions. Briefly, diluted serum samples were incubated with partially purified *H pylori* antigens immobilized on microtiter wells. After washing away unbound serum components, rabbit anti-human immunoglobulin G conjugated to horseradish peroxidase was added to the wells. Unbound conjugate was removed by washing, and a solution containing 3,3′,5,5′-tetramethylbenzidine and enzyme substrate was added to trace specific antibody binding. The optical densities of the standards, controls, and samples were measured using a microplate reader at 450 nm. An index of <0.9 was considered negative, an index of ≥1.1 was considered positive, and values between 0.9 and 1.1 were equivocal. Appropriate positive and negative controls were included in each rack.

Genotyping Assays

We tested for all 3 genotypes at each of 4 single nucleotide polymorphisms (SNPs); 2 in the *IL-1B* gene (*IL-1B −31*, rs1143627; *IL-1B −511*, rs16944), and 2 in the *TNF-α* gene (*TNF-α −308*, rs1800629; *TNF-α −238*, rs361525) using the Sequenom iPLEX protocol (Sequenom, San Diego, CA). The polymerase chain reaction reactions and primer extension reactions were conducted on Sequenom platform as described previously.[36] iPlex products were diluted and desalted with 15 μL sterile water and 3 μL of resin prior to spotting onto a SpectroChip (Sequenom) for analysis in the Compact Mass Spectrometer, using the MassARRAY Workstation software version 3.3 (Sequenom). Genotype accuracy was calculated for all SNPs tested at 99.95%.

Statistical Analysis

We estimated the relative risks of esophageal cancer associated with *H pylori* infection by calculating the odds ratio (OR) and 95% confidence interval (95% CI) using multivariable logistic regression analysis in SAS version 9.1 (SAS Institute, Inc, Cary, NC). Our approach was, first, to fit simple age- and sex-adjusted models for each exposure. We then additionally adjusted for those variables that were significantly associated with risk of esophageal cancers in our data set, namely education, smoking, alcohol consumption, frequency of aspirin/NSAID use, and BMI. Fully adjusted models included the preceding variables as well as a term for frequency of gastroesophageal reflux symptoms.

To explore whether the associations between *H pylori* infection and cancer risk were modified by exposure to known or suspected causal factors, we repeated the above analyses for genotypes at each locus (3 genotypes each for *IL-1B −31* and *IL-1B −511;* combined genotypes for *TNF-α −308*; *TNF-α −238*) and within strata of the frequency of symptoms of gastroesophageal reflux ("never," "less than weekly," "at least weekly"), smoking status ("never", "ever"), and BMI (<25.0, 25.0–29.9, ≥30 [kg/m^2]). To assess the statistical significance of differences in associations across the strata of genotype or host characteristics, we assessed the *P* value for the type III analysis of effects for the interaction terms. For all analyses, statistical significance was determined at $\alpha = .05$, and all tests for statistical significance were 2 sided. The study was approved by the Human Research Ethics Committee of the Queensland Institute of Medical Research and

Table 1. Demographic Characteristics of Controls and Cases of Esophageal Adenocarcinoma, Adenocarcinoma of Esophago-Gastric Junction, and Esophageal Squamous Cell Carcinoma

		Distribution of controls and cases			
Exposure	Category	Control n = 1355 Count (%)	EAC n = 269 Count (%)	EGJAC n = 307 Count (%)	ESCC n = 218 Count (%)
Age, *y*	<49	216 (15)	21 (8)	28 (8)	14 (6)
	50–59	348 (26)	75 (28)	88 (29)	57 (26)
	60–69	480 (35)	103 (39)	100 (33)	78 (36)
	70–79	311 (23)	70 (26)	91 (30)	69 (32)
Sex	Female	459 (34)	22 (8)	38 (12)	92 (42)
	Male	896 (66)	247 (92)	269 (88)	126 (58)
Education	School only	547 (40)	123 (46)	125 (41)	121 (56)
	Tech/diploma	604 (45)	129 (48)	148 (48)	80 (38)
	University	204 (15)	17 (6)	34 (11)	17 (8)
	P value[a]		<.001	.32	<.001
BMI (kg/m^2)	<25	473 (35)	44 (17)	76 (26)	113 (55)
	25–29.9	588 (44)	114 (44)	126 (42)	61 (30)
	≥30	284 (21)	101 (39)	96 (32)	33 (16)
	P value		<.001	<.001	<.001
Smoking history	Never	610 (45)	65 (24)	75 (24)	53 (24)
	1–29 pack-years	516 (38)	109 (41)	128 (42)	82 (38)
	30+ pack-years	229 (17)	95 (35)	104 (34)	82 (38)
	P value		<.001	<.001	<.001
Mean alcohol consumption (standard drinks/week)	None	143 (11)	20 (8)	27 (9)	28 (13)
	<1	86 (6)	6 (2)	12 (4)	13 (6)
	1–6	423 (31)	60 (23)	77 (25)	50 (23)
	7–20	437 (32)	99 (37)	106 (35)	42 (19)
	21+	263 (19)	82 (31)	83 (27)	85 (39)
	P value		<.001	.002	.01
Frequency of symptoms of heartburn or reflux	Never	578 (43)	59 (22)	83 (27)	101 (47)
	<1/week	597 (44)	96 (36)	116 (38)	54 (25)
	≥1/week	174 (13)	112 (42)	107 (35)	59 (28)
	P value		<.001	<.001	.05
Frequency of use of aspirin/NSAIDs past 5 years	Never	276 (20)	63 (23)	78 (25)	43 (20)
	<1/week	711 (52)	126 (49)	153 (50)	121 (57)
	≥1/week	368 (27)	80 (30)	76 (25)	50 (23)
	P value		.92	.09	.48
Self-reported prior *H pylori* infection	No	1237 (93)	248 (93)	278 (91)	194 (90)
	Yes	93 (7)	20 (7)	27 (9)	22 (10)
	P value		.78	.26	.10

EAC, esophageal adenocarcinoma; EGJAC, adenocarcinoma of esophago-gastric junction; ESCC, esophageal squamous cell carcinoma.
[a]*P* value for χ^2 test comparing each group of cases to the controls for the distribution of each categorical variable.

participating hospitals, and all participants gave their informed consent to take part.

Results

Demographic characteristics of cases and controls are shown in Table 1. As anticipated, higher proportions of cases were ever smokers, and reported having had reflux symptoms. The prevalence of overweight and obesity was higher among EAC and EGJAC cases than controls; patients with ESCC were least likely to be overweight or obese.

Predictors of H pylori *Infection Among Controls*

The overall prevalence of *H pylori* antibodies among controls was 23%. The prevalence of *H pylori* seropositivity increased markedly with age (<40 years, 5%; 40–49 years, 12%; 50–59 years, 19%; 60–69 years, 25%; 70–79 years, 31%; *P* trend <.001) and was significantly associated with low levels of education (school only, 28%; technical college, 22%; university, 14%; $P < .001$) and high levels of smoking (never smokers, 21%; 1–29 pack-years, 23%; 30+ pack-years, 29%; *P* trend = .03). We found similar prevalences of seropositivity by sex and across categories of BMI, alcohol intake, and gastroesophageal reflux symptom frequency (not shown).

H pylori *Infection and Risk of Esophageal Cancers*

Patients with EAC and EGJAC were significantly less likely than controls to have antibodies to *H pylori*

Table 2. Relative risks of Esophageal Adenocarcinoma, Adenocarcinoma of Esophago-Gastric Junction, and Esophageal Squamous Cell Carcinoma Associated With *H pylori* Seropositivity

	Controls		Cases		Minimally adjusted		Partially adjusted		Fully adjusted	
H pylori serostatus	N	%	N	%	OR[a]	95% CI	OR[b]	95% CI	OR[c]	95% CI
EAC										
Negative	1014	75	225	84	1.00	Reference	1.00	Reference	1.00	Reference
Positive	302	22	35	13	0.48	0.33–0.71	0.43	0.29–0.64	0.44	0.29–0.67
Equivocal	39	3	9	3	0.77	0.35–1.70	0.68	0.30–1.54	0.70	0.31–1.61
EGJAC										
Negative	1014	75	261	85	1.00	Reference	1.00	Reference	1.00	Reference
Positive	302	22	37	12	0.42	0.29–0.61	0.39	0.26–0.57	0.40	0.27–0.59
Equivocal	39	3	9	3	0.74	0.35–1.57	0.64	0.30–1.39	0.65	0.30–1.42
ESCC										
Negative	1014	75	154	71	1.00	Reference	1.00	Reference	1.00	Reference
Positive	302	22	54	25	1.19	0.84–1.68	1.06	0.74–1.53	1.08	0.74–1.57
Equivocal	39	3	10	5	1.40	0.64–3.08	1.18	0.51–2.75	1.27	0.54–3.01

[a]Odds ratio for *H pylori* +ve vs *H pylori* −ve, adjusted for sex and age.
[b]Odds ratio for *H pylori* +ve vs *H pylori* −ve, adjusted for sex, age, educational level, smoking history, BMI category, mean lifetime alcohol intake, frequency of aspirin/NSAID use in past 5 years.
[c]Odds ratio for *H pylori* +ve vs *H pylori* −ve, adjusted for sex, age, educational level, smoking history, BMI category, mean lifetime alcohol intake, frequency of aspirin/NSAID use in past 5 years, and frequency of reflux/heartburn symptoms in 10 years before study.

(Table 2), whereas the prevalence of seropositivity among patients with ESCC was very similar to controls. Adjustment for potentially confounding factors made little difference to the risk estimates for any of the cancers.

Analyses Stratified by Patient Characteristics

We repeated the multivariable analyses for *H pylori* within strata of known causal factors for esophageal cancer (Table 3). Whereas there was some variability in the magnitude of risk estimates across strata

Table 3. Relative risks of Esophageal Adenocarcinoma, Adenocarcinoma of Esophago-Gastric Junction, and Esophageal Squamous Cell Carcinoma Associated With *H pylori* Seropositivity, Stratified by Other Causal Factors

	EAC		EGJAC		ESCC	
	Odds ratios[a]	95% CI	Odds ratios[a]	95% CI	Odds ratios[a]	95% CI
GER never	0.53	0.23–1.24	0.30	0.13–0.70	0.76	0.41–1.42
GER < weekly	0.40	0.19–0.82	0.43	0.22–0.83	1.63	0.80–3.33
GER ≥ weekly	0.55	0.25–1.20	0.64	0.30–1.35	1.77	0.74–4.26
	P^b = .51		P = .16		P = .20	
Never smoker	0.38	0.13–1.13	0.59	0.27–1.30	1.06	0.43–2.62
1–29 pack-years	0.75	0.40–1.40	0.35	0.17–0.69	1.05	0.55–1.99
30+ pack-years	0.34	0.16–0.73	0.46	0.23–0.91	1.52	0.79–2.92
	P = .23		P = .58		P = .82	
BMI <25	0.95	0.43–2.10	0.40	0.18–0.89	1.01	0.56–1.83
BMI 25–29.9	0.29	0.13–0.61	0.50	0.27–0.91	1.30	0.68–2.50
BMI 30+	0.48	0.24–0.99	0.35	0.16–0.76	1.01	0.37–2.81
	P = .08		P = .71		P = .86	
Never used H2 blockers	0.35	0.21–0.61	0.42	0.27–0.66	0.91	0.56–1.46
Ever used H2 blockers	0.79	0.38–1.63	0.38	0.15–0.97	1.92	0.89–4.13
	P = .05		P = .89		P = .13	
Never used PPI	0.46	0.28–0.75	0.45	0.28–0.71	1.12	0.70–1.78
Ever used PPI	0.63	0.26–1.52	0.47	0.20–1.14	1.41	0.60–3.31
	P = .29		P = .35		P = .98	
Never diagnosed with *H pylori*	0.42	0.27–0.65	0.37	0.24–0.56	1.00	0.65–1.53
Ever diagnosed with *H pylori*	0.76	0.18–3.25	0.80	0.22–2.99	2.19	0.61–7.82
	P = .25		P = .13		P = .05	

GER, gastroesophageal reflux; EAC, esophageal adenocarcinoma; EGJAC, adenocarcinoma of esophago-gastric junction; ESCC, esophageal squamous cell carcinoma.
[a]Odds ratio for *H pylori* +ve vs *H pylori* −ve, adjusted for age, sex, educational level, smoking status, mean lifetime alcohol intake, BMI category, frequency of reflux/heartburn symptoms in 10 years before study, and frequency of aspirin/NSAID use in the past 5 years.
[b]*P* value for the type III analysis of effects for the addition of the interaction term to the saturated model.

of gastroesophageal reflux symptom frequency and cumulative smoking history, these were within the bounds of random variation, and the interaction terms were uniformly nonsignificant. Overall, 7% of population controls and 7%–10% of patients with esophageal cancer reported that they been diagnosed previously with *H pylori*. There was no evidence that the magnitude of the associations between *H pylori* serology and cancer risk differed according to prior diagnosis *H pylori* (not shown). For BMI however, the interaction term included in EAC model approached statistical significance ($P = .08$), although inspection of the stratum-specific risk estimates does not suggest a consistent pattern of effect modification. There was some evidence that the inverse association between *H pylori* and EAC was stronger among those who reported never using H2-antagonists (OR, 0.35) than those who ever reported using them (OR, 0.77) (test for interaction, $P = .05$). There was no statistical evidence for there being a difference in the magnitude of effects for EGJAC or ESCC nor for any of the cancers when stratified by PPI use (Table 3).

Cytokine Genotypes and Risk of Esophageal Cancers

All SNPs were in Hardy–Weinberg equilibrium. Genotype and minor allele frequencies for genes hypothesized to determine host responses to *H pylori* infection are presented in Table 4. Distributions of *IL-1B −31*, *IL-1B −511*, *TNF-α −308*, and *TNF-α −238* among patients with EAC, EGJAC, or ESCC were not statistically significantly different from population controls.

Analyses Stratified by Genotype

In stratified analyses, we found no evidence that the inverse associations between *H pylori* infection and EAC/EGJAC were modified by the presence of polymorphisms at *IL-1B −31*, *IL-1B −511*, *TNF-α −308*, and *TNF-α −238* (Table 5). Similarly, the null associations for ESCC were observed within all genotypic strata.

Discussion

We found that patients with EAC or EGJAC were significantly less likely than population controls to have serologic evidence of *H pylori* infection, whereas patients with ESCC were no different from controls in this respect. For the first time, we assessed whether polymorphisms in the interleukin-1 gene cluster and TNF-α modify the association between *H pylori* infection and risk of cancer. Previous research suggested that these genes greatly influence gastric acid production and thereby modify the carcinogenic potential of *H pylori* infection. We found little evidence to support this hypothesis with respect to cancers of the

Table 4. Genotype frequencies for *IL-1B − 31*, *IL-1B −511*, *TNF-α −308* and *TNF-α −238* Among Controls and Cases of Esophageal Adenocarcinoma, Adenocarcinoma of Esophago-Gastric Junction, and Esophageal Squamous Cell Carcinoma

		Control		EAC		EGJAC		ESCC	
	Genotype	n = 1316	%	n = 260	%	n = 298	%	n = 208	%
IL-1B −31	CC	160	12.5	36	14.2	26	8.9	20	9.7
rs1143627	TC	566	44.2	114	45.1	136	46.4	92	44.4
	TT	555	43.3	103	40.7	131	44.7	95	45.9
	Missing	35		7		5		1	
	MAF		34.8		36.8		32.1		31.9
IL-1B −511	CC	565	43.6	98	41.5	119	44.2	88	44.4
rs16944	CT	591	45.6	106	44.9	127	47.2	90	45.5
	TT	141	10.9	32	13.6	23	8.6	20	10.1
	Missing	19		24		29		10	
	MAF		33.8		36.0		32.2		32.8
TNF-α −308	AA	48	3.7	12	4.7	6	2.0	8	3.9
rs1800629	GA	403	31.2	84	33.2	93	31.5	71	34.3
	GG	842	65.1	157	62.1	196	66.4	128	61.8
	Missing	23		7		3		1	
	MAF		19.2		21.3		17.8		21.0
TNF-α −238	AA	9	0.7	3	1.2	0	0.0	1	0.5
rs361525	GA	125	9.6	32	12.5	26	8.8	23	11.1
	GG	1165	89.7	221	86.3	270	91.2	183	88.4
	Missing	17		4		2		1	
	MAF		5.6		7.4		4.4		6.0
	Total	1316		260		298		208	

MAF, Minor allele frequency; EAC, esophageal adenocarcinoma; EGJAC, adenocarcinoma of esophago-gastric junction; ESCC, esophageal squamous cell carcinoma.

Table 5. Relative Risks of Esophageal Adenocarcinoma, Adenocarcinoma of Esophago-Gastric Junction, and Esophageal Squamous Cell Carcinoma Associated With *H pylori* Seropositivity, Stratified by Genotype

		EAC		EGJAC		ESCC	
Genotype		Odds ratios[a]	95% CI	Odds ratios[a]	95% CI	Odds ratios[a]	95% CI
IL-1B −31	CC	0.62	0.18–2.13	0.49	0.09–2.69	0.75	0.16–3.58
rs1143627	CT	0.34	0.17–0.69	0.29	0.15–0.59	1.00	0.52–1.94
	TT	0.67	0.34–1.31	0.60	0.33–1.09	1.17	0.65–2.12
		P^b = .53		P = .44		P = .76	
IL-1B −511	CC	0.66	0.33–1.32	0.55	0.29–1.03	1.22	0.66–2.24
rs16944	CT	0.35	0.17–0.74	0.34	0.17–0.68	0.95	0.49–1.86
	TT	0.83	0.22–3.10	0.65	0.11–3.80	0.86	0.17–4.26
		P = .38		P = .62		P = .84	
TNF-α −308	AA/GA	0.57	0.27–1.19	0.68	0.34–1.35	1.15	0.57–2.30
rs1800629	GG	0.53	0.30–0.92	0.35	0.20–0.61	1.04	0.62–1.77
		P = .82		P = .12		P = .94	
TNF-α −238	AA/GA	0.39	0.09–1.74	0.35	0.06–2.15	1.18	0.26–5.42
rs361525	GG	0.54	0.34–0.86	0.43	0.28–0.67	1.06	0.68–1.63
		P = .88		P = .95		P = .89	

EAC, esophageal adenocarcinoma; EGJAC, adenocarcinoma of esophago-gastric junction; ESCC, esophageal squamous cell carcinoma.
[a]Odds ratio for *H pylori* +ve vs *H pylori* −ve, adjusted for age, sex, educational level, smoking status, mean lifetime alcohol intake, BMI category, frequency of reflux/heartburn symptoms in 10 years before study, and frequency of aspirin/NSAID use in the past 5 years.
[b]*P* value for the type III analysis of effects for the addition of the interaction term to the saturated model.

esophagus or esophago-gastric junction; the inverse associations observed between *H pylori* and EAC and EGJAC were not significantly different across groups with polymorphisms in *IL-1B −31, IL-1B −511, TNF-α −308*, or *TNF-α −238*. Other factors known to be strongly associated with risk of esophageal adenocarcinomas, including frequency of symptoms of gastroesophageal reflux, smoking, and body mass index, did not substantially modify these associations.

A notable feature of the present study was the overall low prevalence of *H pylori* antibodies. At 23% among controls, the prevalence was less than that observed among comparable population-based studies in Sweden[37] and the United States.[38] The prevalence of *H pylori* infection appears to be declining with successive birth cohorts in Western populations,[39] commonly ascribed to smaller families and improved sanitation and hygiene resulting in lower levels of bacterial colonization during childhood.[40] Seroprevalence data for the Australian population with which to compare our sample are scarce because earlier reports have tended to focus on particular subgroups within the community. The most comprehensive data come from a 2002 survey of 2413 sera retrieved from 37 major diagnostic laboratories around the nation, which reported the prevalence of *H pylori* antibodies at 15%.[41] That sample was restricted to people less than age 60 years however, whereas our sample was predominantly older than 60 years. The age-specific prevalences among people age 50–59 years, the largest overlapping age category between the 2 studies, were similar (this study, 23% vs laboratory survey, 19%). Although the 2 studies differed in design and purpose, their concordant data suggest that the prevalence of *H pylori* infection in the Australian population is markedly lower than in the United States,[42] United Kingdom, and other Western populations.[43]

Notwithstanding the current low prevalence of infection in the Australian population, the 50%–60% risk reductions we observed for EAC were remarkably similar to those reported in other studies.[23,44] Relatively few studies have examined separately those adenocarcinomas occurring at the junction of the esophagus and stomach. The difficulties of determining the precise site of origin of such tumors are well-known and have been outlined previously[45] and no doubt contribute to the differing findings across studies; however, our finding of substantially lower risks of EGJAC cancers associated with *H pylori* is similar to that of Kamangar et al.[46] The definition of cardia cancer used in that study was essentially the same as the definition we used for EGJAC, and it is possible that in both studies this category comprises a mixture of distal EACs, genuine junctional cancers, and some gastric cancers.

We explored whether these inverse associations were confounded or modified by other factors also known to be strongly associated with risk of adenocarcinomas but found no evidence of such effects. Whereas there was a marginally significant difference in the magnitude of the inverse association for EAC between those who self-reported use of H2 antagonists and those who did not, no such effect was seen for PPIs or for EGJAC and ESCC. Of note, we observed lower risks of EAC and EGJAC associated with *H pylori* infection regard-

less of frequency of gastroesophageal reflux, a finding consistent with the notion that *H pylori* may influence cancer risks through pathways other than gastric acid. Host responses to *H pylori* infections are determined, at least in part, by families of cytokines. With respect to gastric cancer, there is strong evidence that SNPs in *IL-1B*, and to a lesser extent *TNF-α*, confer substantially increased risks of the disease, most likely through acid suppression and gastric atrophy.[29] We therefore hypothesized that the same proinflammatory genotypes that inhibit gastric acid in the presence of *H pylori* infection would be especially protective against EAC and EGJAC, but our data provide no support for this hypothesis. One previous study has genotyped patients with EAC and ESCC and controls for these SNPs, and, whereas the tabulated risk estimates for *IL-1B −511* suggested significant positive associations between the TT genotype and both ESCC and EAC, the authors concluded that there was in fact no evidence of an association.[47]

We found no association between evidence of *H pylori* infection with squamous cell cancers of the esophagus. Whereas a number of studies have reported positive associations with infection, particularly with the *cagA+* strain,[37] a recent meta-analysis concluded that there was no association (*cagA+ve* vs *H pylori-ve*: summary OR, 1.01; 95% CI: 0.80–1.27).[23] However, it was noted that there was considerable heterogeneity between studies in the magnitude of associations, although the source was not determined. Adding our data to future meta-analyses would likely strengthen the case for no association.

Is the inverse association between *H pylori* infection and EAC and EGJAC evidence of a biologically protective effect? Several potential mechanisms have been proposed to explain the association, including hypoacidity subsequent to prolonged infection,[48] dysregulation of host cytokine or immune responses, disturbances to microbial flora,[22] and changes in the expression of locally acting hormones relating to obesity pathways (notably leptin and ghrelin).[24,49,50] Each of these hypotheses is plausible, and all may indeed play a role. Assays for other markers of gastric function, notably the ratio of pepsinogens I and II, could be informative in determining whether the protective effect is mediated through gastric atrophy for example. The blood samples collected from participants in this study precluded their use for pepsinogen assays on 2 grounds. First, the interval between collection and processing was greater than 10 hours for most participants, and, second, participants were not fasted prior to blood draw. Two previous studies have reported strongly protective effects of *H pylori* among those without serologic evidence of gastric atrophy however,[37,51] suggesting that this is not the only pathway through which *H pylori* mediates its apparent protective effects. Perhaps the definitive test for a protective role for this organism in EAC/EGJAC would be to examine gastric biopsy samples from study participants for histologic evidence of *H pylori*-induced corpus atrophy. Such biopsy samples were not available for cases or controls in this study but could be considered in future studies. Our stratified analyses failed to identify particular subgroups of the population for whom infection with *H pylori* was more or less protective, and so we have no strong evidence to refute any of the hypotheses above. Indeed, such mechanistic questions involving the interplay of numerous pathways, all of which may interact, may be beyond the resolution of epidemiologic studies.

Whatever the precise mechanism, it seems likely that *H pylori* acts early in the causal pathway to EAC, given the findings of recent studies reporting that patients with Barrett's esophagus, the precancerous precursor to EAC, also have lower rates of *H pylori* infection than the general population.[52] Arguably the most compelling evidence to date comes from a community-based case-control study of *H pylori* and Barrett's esophagus conducted in northern California, a population with similarly low prevalences of *H pylori* infection as we found in Australia.[53] In that study, the overall association with Barrett's esophagus was OR, 0.42; (95% CI: 0.26–0.70), similar in magnitude to the association reported here.

A limitation of the study was the low rates of participation, raising concerns about possibly biased selection of cases and controls. The cases who participated were very similar in age and sex distribution to those notified to the Australian Institute of Health and Welfare; however, further details about the characteristics of non-participating cases were not available because of Australian privacy laws. It is likely that cases with long survival were over-represented in our study sample, but this would apply to all patients with esophageal cancer recruited into the study and could not explain the inverse associations between *H pylori* infection status and EAC and EGJAC. The participation fraction among controls was also less than ideal, and a spurious positive association might be explained if the prevalences of *H pylori* infection or other factors among participating controls were unrepresentative. We have shown that the age-specific prevalence of *H pylori* infection among our controls was similar to the only other recent population study in Australia, and the distribution of BMI was also similar to the Australian National Health Survey 2004, a representative survey of the Australian adult population. Frequent symptoms of reflux were reported by ~12% of controls, remarkably similar to other population surveys.[34,54,55] Whereas we have shown previously that the proportion

of current smokers among our control series was somewhat lower than the population average,[56] this would most likely bias our study towards the null because *H pylori* infection is positively associated with smoking. We therefore consider the likelihood of biased selection on the basis of these factors to be no greater than for previous studies and unlikely to account for the inverse associations we observed.

We cannot exclude misclassification of *H pylori* exposure, particularly false negative results, as an explanation, although the kit we used has a sensitivity of 91% and specificity of 100%. Moreover, for misclassification of *H pylori* infection status to wholly explain these findings would require that patients with EAC and EGJAC, but not ESCC, were incorrectly categorized, a highly improbable scenario. We did not measure antibodies to cag-A, the strain of *H pylori* most closely associated with risks of gastric cancer and for which the inverse associations with EAC have also been noted.[23] Had we measured cag-A status, it is likely that the inverse associations with EAC and EGJAC would have been even more marked.

In summary, we found that the risks of EAC and EGJAC are significantly lower among people with evidence of prior *H pylori* infection and that this appears independent of genotype of the SNPs we have tested and of other host characteristics that are associated with these cancers.

References

1. Ferlay J, Bray F, Pisani P, et al. GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide. International Agency for Research on Cancer, Base No. 5. version 2.0, IARC Press, Lyon, 2004.
2. Blot WJ, McLaughlin JK. The changing epidemiology of esophageal cancer. Semin Oncol 1999;26:2–8.
3. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 2005;97:142–146.
4. Lagergren J, Bergstrom R, Lindgren A, et al. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma (comments). N Engl J Med 1999;340:825–831.
5. Gammon MD, Schoenberg JB, Ahsan H, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia (comments). J Natl Cancer Inst 1997; 89:1277–1284.
6. Kabat GC, Ng SK, Wynder EL. Tobacco, alcohol intake, and diet in relation to adenocarcinoma of the esophagus and gastric cardia. Cancer Causes Control 1993;4:123–132.
7. Kubo A, Corley DA. Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2006;15:872–878.
8. Lagergren J, Bergstrom R, Lindgren A, et al. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. Int J Cancer 2000;85:340–346.
9. Mayne ST, Navarro SA. Diet, obesity and reflux in the etiology of adenocarcinomas of the esophagus and gastric cardia in humans. J Nutr 2002;132:S3467–S3470.
10. Vaughan TL, Davis S, Kristal A, et al. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 1995;4:85–92.
11. Lagergren J. Controversies surrounding body mass, reflux, and risk of oesophageal adenocarcinoma. Lancet Oncol 2006;7:347–349.
12. Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Ann Intern Med 1999;130:883–890.
13. Whiteman DC, Sadeghi S, Pandeya N, et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. Gut 2008;57:173–180.
14. Pandeya N, Williams G, Green AC, et al. Alcohol consumption and the risks of adenocarcinoma and squamous cell carcinoma of the esophagus. Gastroenterology 2009;136:1215–1224.
15. Pandeya N, Williams GM, Sadhegi S, et al. Associations of duration, intensity, and quantity of smoking with adenocarcinoma and squamous cell carcinoma of the esophagus. Am J Epidemiol 2008;168:105–114.
16. Kjaerheim K, Gaard M, Andersen A. The role of alcohol, tobacco, and dietary factors in upper aerogastric tract cancers: a prospective study of 10,900 Norwegian men. Cancer Causes Control 1998;9:99–108.
17. Launoy G, Milan C, Faivre J, et al. Tobacco type and risk of squamous cell cancer of the oesophagus in males: a French multicentre case-control study. Int J Epidemiol 2000;29:36–42.
18. Wei WQ, Abnet CC, Qiao YL, et al. Prospective study of serum selenium concentrations and esophageal and gastric cardia cancer, heart disease, stroke, and total death. Am J Clin Nutr 2004; 79:80–85.
19. Isaacson C. The change of the staple diet of black South Africans from sorghum to maize (corn) is the cause of the epidemic of squamous carcinoma of the oesophagus. Med Hypotheses 2005;64:658–660.
20. Sitas F, Urban M, Stein L, et al. The relationship between anti-HPV-16 IgG seropositivity and cancer of the cervix, anogenital organs, oral cavity and pharynx, oesophagus and prostate in a black South African population. Infect Agent Cancer 2007;2:6.
21. Islami F, Pourshams A, Nasrollahzadeh D, et al. Tea drinking habits and oesophageal cancer in a high-risk area in northern Iran: population based case-control study. BMJ 2009;338:b929.
22. Blaser MJ. Disappearing microbiota: *Helicobacter pylori* protection against esophageal adenocarcinoma. Cancer Prev Res (Phila Pa) 2008;1:308–311.
23. Islami F, Kamangar F. *Helicobacter pylori* and esophageal cancer risk: a meta-analysis. Cancer Prev Res (Phila Pa) 2008;1:329–338.
24. Shiotani A, Miyanishi T, Uedo N, et al. *Helicobacter pylori* infection is associated with reduced circulating ghrelin levels independent of body mass index. Helicobacter 2005;10:373–378.
25. Sykora J, Malan A, Zahlava J, et al. Gastric emptying of solids in children with *H pylori*-positive and *H pylori*-negative non-ulcer dyspepsia. J Pediatr Gastroenterol Nutr 2004;39:246–252.
26. McColl KE, el-Omar E, Gillen D. *Helicobacter pylori* gastritis and gastric physiology. Gastroenterol Clin North Am 2000;29:687–703.
27. Bahmanyar S, Zendehdel K, Nyren O, et al. Risk of oesophageal cancer by histology among patients hospitalised for gastroduodenal ulcers. Gut 2007;56:464–468.
28. McColl KE. *Helicobacter pylori* and oesophageal cancer—not always protective. Gut 2007;56:457–459.
29. El-Omar EM, Carrington M, Chow WH, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. Nature 2000;404:398–402.
30. Jang WH, Yang YI, Yea SS, et al. The −238 tumor necrosis factor-α promoter polymorphism is associated with decreased susceptibility to cancers. Cancer Lett 2001;166:41–46.

31. Gorouhi F, Islami F, Bahrami H, et al. Tumour-necrosis factor-α polymorphisms and gastric cancer risk: a meta-analysis. Br J Cancer 2008;98:1443–1451.
32. Spechler SJ, Dixon MF, Genta R, et al. Adenocarcinoma of the oesophago-gastric junction. In: Hamilton SR, Aaltonen LA, eds. Pathology and genetics. Tumours of the digestive system. WHO classification of tumours. Volume 2. Lyon IARC Press, 2000.
33. Olsen CM, Green AC, Whiteman DC, et al. Obesity and the risk of epithelial ovarian cancer: a systematic review and meta-analysis. Eur J Cancer 2007;43:690–709.
34. Murray L, Johnston B, Lane A, et al. Relationship between body mass and gastro-oesophageal reflux symptoms: The Bristol Helicobacter Project. Int J Epidemiol 2003;32:645–650.
35. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. Ann Intern Med 2005;143:199–211.
36. Doecke J, Zhao ZZ, Pandeya N, et al. Polymorphisms in MGMT and DNA repair genes and the risk of esophageal adenocarcinoma. Int J Cancer 2008;123:174–180.
37. Ye W, Held M, Lagergren J, et al. *Helicobacter pylori* infection and gastric atrophy: risk of adenocarcinoma and squamous-cell carcinoma of the esophagus and adenocarcinoma of the gastric cardia. J Natl Cancer Inst 2004;96:388–396.
38. Wu AH, Crabtree JE, Bernstein L, et al. Role of *Helicobacter pylori* CagA+ strains and risk of adenocarcinoma of the stomach and esophagus. Int J Cancer 2003;103:815–821.
39. Banatvala N, Mayo K, Megraud F, et al. The cohort effect and *Helicobacter pylori*. J Infect Dis 1993;168:219–221.
40. Webb PM, Knight T, Greaves S, et al. Relation between infection with *Helicobacter pylori* and living conditions in childhood: evidence for person to person transmission in early life. BMJ 1994; 308:750–753.
41. Moujaber T, MacIntyre CR, Backhouse J, et al. The seroepidemiology of *Helicobacter pylori* infection in Australia. Int J Infect Dis 2008;12:500–504.
42. Everhart JE, Kruszon-Moran D, Perez-Perez GI, et al. Seroprevalence and ethnic differences in *Helicobacter pylori* infection among adults in the United States. J Infect Dis 2000;181:1359–1363.
43. Thjodleifsson B, Asbjornsdottir H, Sigurjonsdottir RB, et al. Seroprevalence of *Helicobacter pylori* and cagA antibodies in Iceland, Estonia, and Sweden. Scand J Infect Dis 2007;39:683–689.
44. Rokkas T, Pistiolas D, Sechopoulos P, et al. Relationship between *Helicobacter pylori* infection and esophageal neoplasia: a meta-analysis. Clin Gastroenterol Hepatol 2007;5:1413–1417.
45. Nyren O, Blot WJ. *Helicobacter pylori* infection: mainly foe but also friend? J Natl Cancer Inst 2006;98:1432–1434.
46. Kamangar F, Dawsey SM, Blaser MJ, et al. Opposing risks of gastric cardia and noncardia gastric adenocarcinomas associated with *Helicobacter pylori* seropositivity. J Natl Cancer Inst 2006;98:1445–1452.
47. El-Omar EM, Rabkin CS, Gammon MD, et al. Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. Gastroenterology 2003;124:1193–1201.
48. Blaser MJ, Atherton JC. *Helicobacter pylori* persistence: biology and disease. J Clin Invest 2004;113:321–333.
49. Nwokolo CU, Freshwater DA, O'Hare P, et al. Plasma ghrelin following cure of *Helicobacter pylori*. Gut 2003;52:637–640.
50. Roper J, Francois F, Shue PL, et al. Leptin and ghrelin in relation to Helicobacter pylori status in adult males. J Clin Endocrinol Metab 2008;93:2350–2357.
51. Anderson LA, Murphy SJ, Johnston BT, et al. Relationship between *Helicobacter pylori* infection and gastric atrophy and the stages of the oesophageal inflammation, metaplasia, adenocarcinoma sequence: results from the FINBAR case-control study. Gut 2008;57:734–739.
52. Wang C, Yuan Y, Hunt RH. *Helicobacter pylori* infection and Barrett's esophagus: a systematic review and meta-analysis. Am J Gastroenterol 2009;104:491–501.
53. Corley DA, Kubo A, Levin TR, et al. *Helicobacter pylori* infection and the risk of Barrett's oesophagus: a community-based study. Gut 2008;57:727–733.
54. Watson DI, Lally CJ. Prevalence of symptoms and use of medication for gastroesophageal reflux in an Australian community. World J Surg 2009;33:88–94.
55. Nilsson M, Johnsen R, Ye W, et al. Prevalence of gastro-oesophageal reflux symptoms and the influence of age and sex. Scand J Gastroenterol 2004;39:1040–1045.
56. Pandeya N, Williams GM, Green AC, et al. Do low control response rates always affect the findings? Assessments of smoking and obesity in two Australian case-control studies of cancer. Aust N Z J Public Health 2009;33:312–319.

Received August 13, 2009. Accepted April 1, 2010.

Reprint requests

Address requests for reprints to: David Whiteman, MBBS, PhD, head, Cancer Control Laboratory Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Queensland 4029, Australia. e-mail: david.whiteman@qimr.edu.au; fax (61) 7 3845 3502.

Acknowledgments

The Australian Cancer Study: Oesophageal Cancer.

Investigators: David C. Whiteman, MBBS, PhD; Penelope M. Webb, MA, DPhil; Adele C. Green, MBBS, PhD; Nicholas K. Hayward, PhD; Peter G. Parsons, PhD; David M. Purdie, PhD. Clinical collaborators: B. Mark Smithers, FRACS; David Gotley, FRACS, PhD; Andrew Clouston, FRACP, PhD; Ian Brown, FRACP. Project manager: Suzanne Moore RN, MPH. Database: Karen Harrap, BIT, Troy Sadkowski BIT. Research nurses: Suzanne O'Brien, RN, MPH; Ellen Minehan, RN; Deborah Roffe, RN; Sue O'Keefe, RN; Suzanne Lipshut, RN; Gabby Connor, RN; Hayley Berry, RN; Frances Walker, RN; Teresa Barnes, RN; Janine Thomas, RN; Linda Terry, RN, MPH; Michael Connard, BSc; Leanne Bowes, BSc; MaryRose Malt, RN; Jo White, RN. Laboratory assistants: Lauren Aoude, BEng; Peter Schultz, BSc; Loralie Parsonson, BSc; Stephen Walsh, BSc. Clinical contributors: Australian Capital Territory: Charles Mosse, FRACS; Noel Tait, FRACS; New South Wales: Chris Bambach, FRACS; Andrew Biankan, FRACS; Roy Brancatisano, FRACS, Max Coleman FRACS, Michael Cox FRACS, Stephen Deane FRACS; Gregory L. Falk, FRACS; James Gallagher, FRACS; Mike Hollands, FRACS; Tom Hugh, FRACS; David Hunt, FRACS; John Jorgensen, FRACS; Christopher Martin, FRACS; Mark Richardson, FRACS; Garrett Smith, FRACS; Ross Smith, FRACS; David Storey, FRACS. Queensland: John Avramovic, FRACS; John Croese, FRACP; Justin D'Arcy, FRACS; Stephen Fairley, FRACP; John Hansen, FRACS; John Masson, FRACP; Les Nathanson, FRACS; Barry O'Loughlin, FRACS; Leigh Rutherford, FRACS; Richard Turner, FRACS; Morgan Windsor, FRACS. South Australia: Justin Bessell, FRACS; Peter Devitt, FRACS; Glyn Jamieson, FRACS; David Watson, FRACS. Victoria: Stephen Blamey, FRACS; Alex Boussioutas, FRACP; Richard Cade, FRACS; Gary Crosthwaite, FRACS; Ian Faragher, FRACS; John Gribbin, FRACS; Geoff Hebbard, FRACP; George Kiroff, FRACS; Bruce Mann, FRACS; Bob Millar, FRACS; Paul O'Brien, FRACS; Robert Thomas, FRACS; Simon Wood, FRACS. Western Australia: Steve Archer, FRACS; Kingsley Faulkner, FRACS; Jeff Hamdorf, FRACS.

The authors thank Shahram Sadeghi, MD, PhD, and Harish Babu, MD, for their assistance with pathology abstractions and Nirmala Pandeya, M Med Sc, provided assistance with data cleaning and statistical programming.

Conflicts of interest

The authors disclose no conflicts.

Funding

Supported by the Cancer Council Queensland and the National Health and Medical Research Council (NHMRC) of Australia (Program No. 199600) and by Research Fellowships from the National Health and Medical Research Council of Australia (to N.K.H., G.W.M., and P.M.W.) and Australian Research Council (D.C.W.). The funding bodies played no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

Aspirin, Nonsteroidal Anti-inflammatory Drugs, and the Risks of Cancers of the Esophagus

Shahram Sadeghi,[1,2] Christopher J. Bain,[2] Nirmala Pandeya,[1,2] Penelope M. Webb,[1] Adèle C. Green,[1] and David C. Whiteman[1] for the Australian Cancer Study

[1]Queensland Institute of Medical Research and [2]School of Population Health, University of Queensland, Brisbane, Queensland, Australia

Abstract

Background: **Frequent consumption of aspirin and nonsteroidal anti-inflammatory drugs (NSAID) has been associated with reduced occurrence of cancers of the esophagus, although potential modifying effects of other causal factors remain relatively unexplored.**

Methods: **We compared nationwide samples of Australian patients with adenocarcinomas of the esophagus (EAC; *n* = 367) or esophagogastric junction (EGJAC; *n* = 426) or esophageal squamous cell carcinoma (ESCC; *n* = 309) with control participants sampled from a population register (*n* = 1,580). Intakes of aspirin, other NSAIDs, and acetaminophen (paracetamol) were assessed from self-reports. We calculated odds ratios (OR) and 95% confidence intervals (95% CI) using multivariable logistic regression.**

Results: **Compared with never-users of aspirin, those who used aspirin at least weekly had significantly lower risks of EAC (OR, 0.48; 95% CI, 0.32-0.72), EGJAC (OR, 0.71; 95% CI, 0.49-1.01), and ESCC (OR, 0.63; 95% CI, 0.40-0.98). At least weekly use of other NSAIDs was also associated with reduced risks of EAC (OR, 0.74; 95% CI, 0.51-1.08), EGJAC (OR, 0.53; 95% CI, 0.37-0.77), and ESCC (OR, 0.46; 95% CI, 0.30-0.73). No association was observed between frequent use of acetaminophen and esophageal cancer. Risk reductions for EAC among users of aspirin and NSAIDs were greater among those who experienced at least weekly symptoms of reflux (OR, 0.26; 95% CI, 0.12-0.55 and OR, 0.41; 95% CI, 0.21-0.77, respectively) than those who did not experience reflux (OR, 0.96; 95% CI, 0.46-2.00 and OR, 0.78; 95% CI, 0.35-1.72, respectively). Recent use of NSAIDs in the past 5 years was associated with greater risk reductions.**

Conclusions: **Frequent use of aspirin and NSAIDs is associated with reduced occurrence of esophageal cancers, particularly among those with frequent symptoms of gastroesophageal reflux.** (Cancer Epidemiol Biomarkers Prev 2008;17(5):1169–78)

Introduction

Worldwide, cancers of the esophagus are the fourth leading cause of death from cancer (1). The two main histologic types of esophageal cancer, namely squamous cell carcinoma (ESCC) and adenocarcinoma (EAC), are characterized by different patterns of occurrence and different causal mechanisms. Until recently, almost all esophageal cancers were of the squamous subtype; however, during the past three decades, the incidence of esophageal adenocarcinomas has increased rapidly, especially in Western countries. Indeed, in some populations, the rates of esophageal adenocarcinoma are increasing faster than for any other major cancer (2). Despite efforts to improve methods for detection and to develop better treatments, the overall 5-year survival for both types of esophageal cancer remains around 5% to 23% (3-5).

For ESCC, the major causal factors in Western popuations are high levels of smoking and alcohol consumption (6-10). Other factors such as poor diet, chronic mucosal irritation, infection with human papilloma virus, and, to a lesser extent, genetic predisposition, have also been implicated (11-16). The principal risk factors for EAC include gastroesophageal acid reflux (17), smoking (8, 18), and obesity (9, 19-23).

Because of the increasing incidence of esophageal adenocarcinoma and the very high mortality associated with the disease, strategies to control this cancer through chemoprevention are being urgently explored. One focus of attention has been aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) as possible chemopreventives of a range of epithelial cancers, including cancers of the esophagus (24). This class of medications inhibits the activity of the cyclooxygenase (COX) enzymes (both constitutional COX-1 and inducible COX-2 isoenzymes). COX-2 is overexpressed in many epithelial cancers, including esophageal cancers (25-37). With regard to tumor growth, COX-2 enzyme functions to reduce cellular adhesion and apoptosis and increase angiogenesis (38-40). There is evidence from animal studies that inhibiting the COX-2 enzyme reduces the growth of early esophageal cancers (41-43).

Received 12/4/07; revised 2/8/08; accepted 2/20/08.

Grant support: Queensland Cancer Fund and the National Health and Medical Research Council of Australia (program no. 199600). David Whiteman and Penelope Webb are supported by Senior Research Fellowships from the National Health and Medical Research Council of Australia. Shahram Sadeghi and Nirmala Pandeya are supported by Ph.D. scholarships from the Ministry of Health and Medical Education of IR Iran and the National Health and Medical Research Council of Australia, respectively. The funding bodies played no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

Requests for reprints: David C. Whiteman, Division of Population Studies and Human Genetics, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Brisbane, Queensland 4029, Australia. Phone: 61-7-3362-0279; Fax: 61-7-3845-3502. E-mail: david.whiteman@qimr.edu.au

doi:10.1158/1055-9965.EPI-07-2852

Epidemiologic studies have reported significantly lower risks of esophageal cancer among those who frequently consume aspirin or NSAIDs (10, 44-47) compared with never users; however, it is not known whether the inverse relationship is modified by other causal factors or whether the duration or timing of NSAID intake is important in determining risk reduction. To address these issues, we analyzed data from a population-based case-control study conducted in Australia.

Materials and Methods

Approval to undertake the study was obtained from the research ethics committees of the Queensland Institute of Medical Research and participating hospitals. We obtained written informed consent from all participants.

Participants. Detailed descriptions of the methods for this case-control study have been published previously (23). Briefly, eligible patients were those aged 18 to 79 years with a histologically confirmed primary invasive adenocarcinoma or squamous cell carcinoma of the esophagus or esophagogastric junction diagnosed from July 1, 2001, until June 30, 2005. We identified 1,610 potentially eligible patients attending treatment centers during the study period. Of these, doctors refused contact with 71 patients and 167 died before consent could be obtained. Patients who were too ill (91), were mentally incapable (23), could not read or write in English (41), or could not be contacted (26) were excluded. The remaining 1,191 patients were invited to participate, and, of these, 928 (78% of those approached) agreed to take part. A further 739 living and eligible patients were identified through population-based cancer registries in each state. Of these, treating doctors refused contact for 84; 37 were incapable of taking part; and 232 were unable to be contacted. The remaining 386 registry patients were invited to take part in the study, of whom 253 agreed. Thus, 1,181 of 2,349 patients with esophageal cancer (50.2%) consented to take part in the study. Questionnaires were returned by 1,102 patients (367 and 426 with adenocarcinomas of the esophagus and gastroesophageal junction, respectively, and 309 patients with squamous cell carcinomas).

We prospectively sampled potential controls from the Australian Electoral Roll (enrollment is compulsory) within strata of age (in 5-year age groups) and state of residence to match the distribution of the case series. We aimed for similar numbers of male cases and controls in each stratum of age and state; female controls were intentionally oversampled at all ages to accommodate their simultaneous enrollment in a parallel case-control study of ovarian cancer (48). Of 3,258 potentially eligible control participants who were contacted and invited to participate, 175 were excluded because they were deceased (16), too ill (61), or unable to read or write in English (98), and 41 were lost to follow-up in the interval between initial contact and participation. Of 3,042 remaining controls, 1,680 (55%) accepted. Completed questionnaires were returned by 1,580 controls (48% of all potentially eligible controls selected from the roll).

Details of the histologic type and anatomic site of each tumor were abstracted from diagnostic pathology reports. Anatomic sites of tumors were categorized according to the WHO classification (49) into ''esophageal'' and ''esophagogastric junction'' tumors.

Measurement of Analgesic Exposure. Our aim was to estimate separately the relative risks of EAC, EGJAC, and ESCC associated with exposure to aspirin, NSAIDs, and acetaminophen (paracetamol)—a widely used analgesic that shares similar clinical indications to NSAIDs but has no known associations with cancer. Simple measures of medication consumption were assessed through a structured, self-completed questionnaire; further details of consumption were collected at interview by trained research nurses. Thus, the self-completed questionnaire asked participants to report separately their frequency of use of aspirin, NSAIDs, and acetaminophen during the past 5 years. To aid recall, names of commonly available brands of each class of medication were listed. Frequency of use was elicited on an 8-point scale (''never,'' ''occasionally,'' ''less than once a month,'' ''2 to 3 times per month,'' ''once a week,'' ''2 to 3 times per week,'' ''4 to 7 times per week,'' ''2 or more times per day''). For analysis, these were collapsed to four categories (''never,'' ''less than monthly,'' ''less than weekly,'' ''weekly or more often''). A separate set of questions then asked participants to indicate whether they had ever taken any of 12 separately itemized NSAID medications; these questions included the generic name and all brand names licensed for use in Australia at the time. Positive responses to the latter questions prompted a series of questions during a standardized telephone interview conducted by a trained research nurse.

At interview, we asked respondents to report their ages at first and last use for each NSAID, their pattern of use (either ''regular,'' consumption of NSAIDs at least once a week for duration of 6 months or more, or ''occasional''), as well as their frequency of consumption during periods of use, duration of use, and typical dose during each of four periods (last year, 1-5 years ago, 6-10 years ago, and >10 years ago). Recency of intake was determined regardless of whether the pattern of intake was occasional or regular. Medication interviews were introduced to the data collection protocol in January 2003; participants recruited before 2003 were not interviewed. Interview data were available for 787 controls, 142 EAC cases, 147 EGJAC cases, and 93 ESCC cases. When analyzing measures of lifetime use, we excluded all exposures to NSAIDs reported in the past year.

Measurement of Potential Confounders. In addition to background information about each participant's educational history, usual occupation, and income, the questionnaire asked for details of their height and weight at various times to enable calculation of corresponding body mass index (BMI) by dividing weight in kilograms by the square of height in meters. We used standard WHO categories for analysis (''healthy weight'' <25.0 kg/m^2; ''overweight'' 25.0-29.9 kg/m^2; ''obese'' ≥ 30 kg/m^2). Participants were asked whether, over their whole life, they had ever smoked >100 cigarettes, cigars, or pipes; positive responses elicited further questions regarding consumption and duration of smoking. We derived the number of pack-years of tobacco exposure by dividing the number of cigarettes smoked on a typical day by 20 and multiplying by the total number of years smoked. We asked participants to report the frequency

with which they consumed different classes of alcohol (light beer, regular beer, white wine, red wine, port/sherry, and spirits/liqueurs) at ages 20-29, 30-49 and ≥50 years, as applicable. For these analyses, total alcohol consumption was summed across all age groups for all types of alcohol, from which we calculated a weighted average number of standard drinks (10 g ethanol) consumed per week between age 20 years and current age. We assessed the frequency of symptoms of gastroesophageal reflux 10 years before diagnosis, defined as the presence of heartburn (''a burning pain behind the breastbone after eating'') or acid reflux (''a sour taste from acid or bile rising up into the mouth or throat''). For analysis, we used the highest reported frequency for either symptom and, consistent with previous reports, defined ''frequent symptoms'' as those occurring at least weekly during the 10 years before diagnosis (50, 51).

Statistical Analyses. We calculated the odds ratio (OR) and 95% confidence interval (95% CI) associated with each exposure using multivariable logistic regression analysis in SAS version 9.1 (SAS Institute, Inc.). Our approach was first to fit minimally adjusted models that contained terms for each exposure and the sampling variables (sex, age, and state). We then estimated relative risks associated with each class of aspirin, NSAIDs, and acetaminophen adjusted for these variables and income, smoking, alcohol consumption, and BMI. Fully adjusted models were fitted, which included the preceding variables as well as a term for frequency of gastroesophageal reflux symptoms. For each variable, the lowest category was the reference category. We also assessed the potential confounding effects of antacid medications including proton pump inhibitors, but as these terms made no material difference to the risk estimates, they were not included in the final models. We tested for trend by including categorical measures of analgesic use as ordinal variables (excluding the ''never users'') in the multivariable model and examining the Wald test.

To explore whether the inverse associations between aspirin and NSAID consumption were modified by the effects of known causal factors, we repeated the above analyses after stratifying by the frequency of symptoms of gastroesophageal reflux (never, less than weekly, at least weekly), smoking status (never, ever), and BMI (<25.0 kg/m^2, 25.0-29.9 kg/m^2, ≥30 kg/m^2). We included an interaction term in the full model to assess the statistical significance of the differences in association across strata. Statistical significance was determined at $\alpha = 0.05$, and all tests for statistical significance were two sided.

Results

Characteristics of cases and controls are presented in Table 1. Younger females were overrepresented in the control series owing to their simultaneous recruitment for parallel studies of ovarian cancer; hence, all analyses were adjusted for age in years and sex. As expected, controls differed from each of the cases groups for their distribution of acid reflux symptoms, smoking status, and BMI. Overall, mean weekly alcohol consumption differed little between controls and patients with adenocarcinoma; ESCC cases were more likely to have higher levels of alcohol consumption than controls.

Use of Aspirin, NSAIDs, and Acetaminophen in the Past 5 Years. In minimally adjusted analyses, EAC cases were less likely than controls to report using aspirin occasionally or at least weekly during the past 5 years (Table 2). After adjusting for other confounding factors, weekly users of aspirin during the past 5 years had significantly lower risks of EAC than never users (OR, 0.48; 95% CI, 0.32-0.73). Frequent use of NSAIDs during the past 5 years was also associated with reduced risks of EAC, although this was not statistically significant. When considered together, we found those who used either aspirin or NSAIDs or both more than weekly had significantly lower risks of EAC (OR, 0.55; 95% CI, 0.37-0.81). Use of acetaminophen was widespread among controls and EAC cases, and we found no association between use of this medication and EAC.

Patients with EGJAC were less likely than controls to consume aspirin or NSAIDs during the past 5 years and this was particularly evident at high frequencies of consumption (at least weekly aspirin OR, 0.70; 95% CI, 0.49-1.01; at least weekly NSAIDs OR, 0.53; 95% CI, 0.37-0.77; at least weekly aspirin or NSAIDs OR, 0.59; 95% CI, 0.41-0.84). As for EAC, we found no evidence that use of acetaminophen was associated with occurrence of EGJAC.

There was some evidence that patients with ESCC of the esophagus were less likely than controls to consume aspirin at least weekly, although lower levels of aspirin intake were similarly prevalent among ESCC cases and controls (Table 2). NSAID consumption during the past 5 years was less common among ESCC cases than controls; this was observed at all levels of intake and was statistically significant for the highest level of consumption (OR, 0.46; 95% CI, 0.30-0.73). More than weekly use of either aspirin or NSAIDs or both was associated with significantly lower risks of ESCC (OR, 0.54; 95% CI, 0.36-0.83). Again, use of acetaminophen was highly prevalent and similarly distributed among controls and ESCC cases.

The principal confounding factors differed for each of the three cancer types: For EAC, the greatest effects on risk estimates occurred after including terms for reflux and BMI, whereas for EJGAC, inclusion of terms for reflux and smoking produced the greatest changes to the estimates. For ESCC, the inclusion of terms for smoking and reflux had the greatest effects (data not shown).

Stratified Analyses. We examined the associations between aspirin use and risks of EAC, EGJAC, and ESCC after stratifying by the frequency of symptoms of gastroesophageal acid reflux (Table 3), smoking, and BMI (not shown). We found no association between aspirin consumption and EAC among those who reported never experiencing symptoms of reflux (at least weekly aspirin OR, 0.96; 95% CI, 0.46-2.00). Among the two strata of participants with reflux symptoms, however, we found substantially lower risks of EAC associated with at least weekly use of aspirin (less than weekly reflux stratum OR, 0.52; 95% CI, 0.26-1.00; at least weekly reflux stratum OR, 0.26; 95% CI, 0.12-0.55). Inconsistent patterns across strata of reflux were observed for the association between aspirin consumption and EGJAC or ESCC. For each separate cancer (EAC, EGJAC, and

Table 1. Characteristics of control participants and patients with EAC, EGJAC, and ESCC

Variable	Controls (1,580)	EAC (367)	EGJAC (426)	ESCC (309)	All cases (1,102)
Category	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Age*	60.5 (11.7)	63.7 (9.7)	63.3 (9.3)	64.7 (9.4)	63.5 (9.4)
Gender					
Female	540 (34)	37 (10)	56 (13)	133 (43)	226 (21)
Male	1,040 (66)	330 (90)	370 (87)	176 (57)	876 (80)
Education					
Not finished high school	646 (41)	168 (46)	171 (40)	175 (56)	514 (47)
Finished high school	688 (44)	174 (47)	208 (49)	105 (34)	487 (44)
University	242 (15)	23 (6)	45 (11)	27 (9)	95 (9)
Missing	4 (0.3)	2 (0.5)	2 (0.5)	2 (0.6)	6 (1)
Reflux†					
Never	698 (44)	82 (22)	120 (28)	143 (46)	345 (31)
<Monthly	465 (29)	43 (12)	63 (15)	41 (13)	147 (13)
<Weekly	221 (14)	85 (23)	87 (20)	40 (13)	212 (19)
>Weekly	127 (8)	82 (22)	97 (23)	45 (15)	224 (20)
Daily	57 (4)	71 (19)	56 (13)	36 (12)	163 (15)
Missing	12 (1)	4 (1)	3 (1)	4 (1)	11 (1)
Smoking pack-years					
Never	710 (45)	94 (26)	97 (23)	78 (25)	269 (24)
<15	395 (25)	73 (20)	86 (20)	61 (20)	220 (20)
15-29.9	207 (13)	69 (19)	94 (20)	56 (18)	219 (20)
30+	268 (17)	131 (36)	150 (35)	112 (36)	392 (36)
Missing	0	0	0	2 (1)	2 (0)
Maximum ever BMI‡ (kg/m^2)					
<25	365 (23)	40 (11)	55 (13)	117 (38)	212 (19)
25-30	708 (45)	136 (37)	178 (42)	109 (35)	423 (38)
30.1-35	333 (21)	114 (31)	122 (29)	52 (17)	288 (26)
>35	159 (10)	67 (18)	62 (14)	20 (6)	149 (14)
Missing	15 (1)	10 (3)	9 (2)	11 (4)	30 (3)
Weekly alcohol consumption units 10 g alcohol					
Never	234 (15)	33 (9)	39 (9)	45 (15)	117 (11)
0-4.5	409 (26)	68 (19)	92 (22)	62 (20)	222 (20)
4.6-10.5	334 (21)	71 (21)	88 (21)	40 (13)	199 (18)
10.6-23.5	352 (22)	101 (28)	109 (26)	58 (19)	268 (24)
>23.5	247 (16)	93 (25)	98 (23)	102 (33)	293 (27)
Missing	0	1 (0)	0	2 (1)	3 (0.3)

*Mean age ± SD.
†History of gastroesophageal reflux symptoms 10 y before diagnosis.
‡Body mass index.

ESCC), we found consistently that the greatest risk reductions associated with NSAID consumption were observed among those who experienced frequent reflux symptoms (Table 3). When we conducted similar analyses across strata of smoking and BMI, we observed similar inverse associations with aspirin and NSAIDs among nonsmokers and smokers and across all BMI categories (data not shown). Similarly, we found no evidence that associations with either aspirin or NSAIDs differed by age or sex for any of the cancer types (data not shown).

Lifetime Use of NSAIDs. Detailed assessments of lifetime patterns and frequency of NSAID use (but not aspirin or acetaminophen) were collected at interview. Among controls, the most frequently reported classes of NSAIDs were ibuprofen (23%) followed by diclofenac (19%), celecoxib (14%), naproxen (9%), indomethacin (8%), and piroxicam (6%). Patients with esophageal cancer were significantly less likely than controls to report ever using NSAIDs during their life (Table 4), with risk estimates of similar magnitude for all three types of cancer. Both occasional and regular users of NSAIDs had lower risks of esophageal cancers than never users; however, risks were uniformly lower for those who reported regular use of NSAIDs (defined as ''at least weekly NSAID use for at least 6 months''). The greatest risk reduction was observed for ESCC among regular users of NSAIDs (OR, 0.21; 95% CI, 0.13-0.33). We found some evidence that use of NSAIDs 1 and 5 years ago was associated with lower risks of esophageal cancers than use more than 5 years ago, although for both periods of use, risks of cancer were significantly lower than for those who never used NSAIDs. There was no effect of duration of exposure to NSAIDs in our data; associations of esophageal cancers with less or more than 5 years use of NSAIDs were similar. When the pattern and duration of NSAID intake were assessed together, there was no evidence that risks of either EAC or ESCC among regular users of NSAIDs differed with duration of consumption. For EGJAC, on the other hand, there was a monotonic reduction in risk from occasional use for 5 years or less (OR, 0.70; 95% CI, 0.47-1.05) toward regular use for more than 5 years (OR, 0.25; 95% CI, 0.14-0.43; P_{trend} <0.0001).

Discussion

This is one of the largest studies to have examined the association between consumption of anti-inflammatory and analgesic medications and esophageal cancers. Novel features of this study were the simultaneous

Table 2. Relative risks of esophageal cancers associated with use of aspirin, NSAIDs, or acetaminophen in last 5 y, minimally and fully adjusted

	Controls	Cases	Minimally* adjusted	Fully † adjusted
	n (%)	*n* (%)	OR (95% CI)	OR (95% CI)
EAC				
Aspirin	1,580	367		
Never	638 (40)	159 (44)	1 (Reference)	1 (Reference)
Occasionally	553 (35)	101 (28)	0.65 (0.49-0.87)	0.62 (0.45-0.86)
Less than weekly	154 (10)	52 (14)	1.24 (0.86-1.88)	1.28 (0.83-1.96)
At least weekly	232 (15)	52 (14)	0.69 (0.48-0.98)	0.48 (0.32-0.73)
Missing	3 (0.2)	3 (0.1)		
P_{trend}			0.35	0.48
NSAIDs				
Never	691 (44)	174 (47)	1 (Reference)	1 (Reference)
Occasionally	488 (31)	92 (25)	0.77 (0.58-1.03)	0.76 (0.55-1.05)
Less than weekly	153 (10)	28 (8)	0.76 (0.49-1.19)	0.65 (0.39-1.07)
At least weekly	240 (15)	70 (19)	1.14 (0.83-1.59)	0.74 (0.51-1.08)
Missing	8 (1)	3 (1)		
P_{trend}			0.04	0.91
Aspirin and NSAIDs				
Never	307 (19)	83 (23)	1 (Reference)	1 (Reference)
Occasionally	599 (38)	111 (30)	0.68 (0.49-0.94)	0.68 (0.47-0.98)
Less than weekly	249 (16)	64 (17)	0.96 (0.65-1.40)	0.90 (0.58-1.39)
At least weekly	422 (27)	108 (29)	0.82 (0.58-1.14)	0.55 (0.37-0.81)
Missing	3 (0.2)	1 (0.2)		
P_{trend}			0.17	0.37
Acetaminophen				
Never	180 (12)	44 (12)	1 (Reference)	1 (Reference)
Occasionally	809 (51)	168 (46)	1.03 (0.70-1.52)	0.94 (0.61-1.45)
Less than weekly	413 (26)	96 (26)	1.33 (0.87-2.10)	1.31 (0.81-2.10)
At least weekly	177 (11)	59 (16)	1.72 (1.09-2.72)	0.85 (0.50-1.44)
Missing	1 (0.1)	0 (0)		
P_{trend}			<0.01	0.76
EJGAC				
Aspirin		426		
Never	638 (40)	171 (40)	1 (Reference)	1 (Reference)
Occasionally	553 (35)	142 (34)	0.88 (0.67-1.13)	0.89 (0.67-1.17)
Less than weekly	154 (10)	40 (10)	0.92 (0.62-1.37)	0.89 (0.58-1.38)
At least weekly	232 (15)	70 (16)	0.91 (0.65-1.26)	0.70 (0.49-1.01)
Missing	3 (0.2)	3 (0.7)		
P_{trend}			0.99	0.26
NSAIDs				
Never	691 (44)	216 (51)	1 (Reference)	1 (Reference)
Occasionally	488 (31)	114 (27)	0.80 (0.61-1.04)	0.75 (0.56-1.00)
Less than weekly	153 (10)	34 (8)	0.75 (0.50-1.13)	0.61 (0.39-0.97)
At least weekly	240 (15)	57 (13)	0.76 (0.54-1.06)	0.53 (0.37-0.77)
Missing	8 (1)	5 (1)		
P_{trend}			0.95	0.08
Aspirin and NSAIDs				
Never	307 (19)	93 (22)	1 (Reference)	1 (Reference)
Occasionally	599 (38)	160 (38)	0.89 (0.66-1.20)	0.89 (0.64-1.24)
Less than weekly	249 (16)	55 (13)	0.75 (0.51-1.10)	0.72 (0.48-1.11)
At least weekly	422 (27)	117 (27)	0.82 (0.59-1.12)	0.59 (0.41-0.84)
Missing	3 (0.2)	1 (0.2)		
P_{trend}			0.47	<0.01
Acetaminophen				
Never	180 (12)	48 (12)	1 (Reference)	1 (Reference)
Occasionally	809 (51)	214 (50)	1.14 (0.79-1.63)	1.04 (0.71-1.54)
Less than weekly	413 (26)	96 (23)	1.11 (0.75-1.66)	1.00 (0.64-1.55)
At least weekly	177 (11)	67 (16)	1.65 (1.07-2.55)	1.03 (0.64-1.70)
Missing	1 (0.1)	1 (0)		
P_{trend}			0.09	0.84
ESCC				
Aspirin	1,580	309		
Never	638 (40)	125 (41)	1 (Reference)	1 (Reference)
Occasionally	553 (35)	111 (36)	1.03 (0.81-1.43)	1.09 (0.79-1.50)
Less than weekly	154 (10)	28 (9)	1.11 (0.73-1.82)	1.32 (0.79-2.23)
At least weekly	232 (15)	39 (13)	0.69 (0.48-1.07)	0.63 (0.40-0.98)

(*Continued on the following page*)

Table 2. Relative risks of esophageal cancers associated with use of aspirin, NSAIDs, or acetaminophen in last 5 y, minimally and fully adjusted (Cont'd)

	Controls	Cases	Minimally* adjusted	Fully† adjusted
	n (%)	*n* (%)	OR (95% CI)	OR (95% CI)
Missing	3 (0.2)	6 (2)		
P_{trend}			0.06	0.04
NSAIDs				
Never	691 (44)	159 (52)	1 (Reference)	1 (Reference)
Occasionally	488 (31)	83 (27)	0.82 (0.61-1.10)	0.89 (0.64-1.23)
Less than weekly	153 (10)	19 (6)	0.64 (0.38-1.07)	0.62 (0.34-1.11)
At least weekly	240 (15)	38 (12)	0.62 (0.42-0.91)	0.46 (0.30-0.73)
Missing	8 (1)	10 (3)		
P_{trend}			0.14	0.01
Aspirin and NSAIDs				
Never	307 (19)	71 (23)	1 (Reference)	1 (Reference)
Occasionally	599 (38)	123 (40)	0.99 (0.71-1.38)	1.03 (0.71-1.49)
Less than weekly	249 (16)	37 (12)	0.82 (0.53-1.28)	0.96 (0.59-1.59)
At least weekly	422 (27)	72 (23)	0.66 (0.45-0.95)	0.54 (0.36-0.83)
Missing	3 (0.2)	6 (2)		
P_{trend}			0.01	<0.01
Acetaminophen				
Never	180 (12)	26 (8)	1 (Reference)	1 (Reference)
Occasionally	809 (51)	176 (57)	1.57 (1.01-2.46)	1.67 (1.01-2.75)
Less than weekly	413 (26)	52 (17)	1.02 (0.61-1. 70)	1.15 (0.65-2.03)
At least weekly	177 (11)	50 (16)	1.73 (1.02-2.92)	1.26 (0.69-2.29)
Missing	1 (0.1)	5 (2)		
P_{trend}			0.57	0.10

*Adjusted for age (in years) and sex.
†Adjusted for age (in years), sex, state of residence, household income, cumulative smoking history, mean alcohol consumption, BMI and frequency of gastroesophageal reflux symptoms 10 y before diagnosis.

analysis of cancers of the esophagus and esophagogastric junction of different histologic types; the collection of detailed information about duration, recency, and patterns of intake of aspirin and NSAIDs; and the collection of information about exposure to acetaminophen (a widely used analgesic that shares many of the same clinical indications as aspirin and NSAIDs). Overall, we found that people who reported regular use of aspirin or NSAIDs had lower risks of all types of esophageal cancer than people who reported never using these medications, whereas people who regularly used acetaminophen had similar risks to people who did not use the medication.

Our study had several strengths. First, our population-based sample was large, enhancing precision of risk estimates and allowing us to perform stratified analyses to assess effect modification. Second, we had detailed measures of exposure based on personal interviews, including measures of different aspects of consumption such as pattern, duration, and recency of intake. Third, neither participants nor interviewers were informed of the study hypotheses, minimizing the possibility of biased recall. The lack of effect with acetaminophen for any of the cancers accords with earlier findings (45) and underscores our confidence that biased recall is unlikely to account for the observed effects.

A weakness of our study was the low rates of participation, raising concerns about possibly biased selection of cases and controls. The age and sex distribution of the cases who took part was similar to the annual distribution of cases notified to the Australian National Cancer Statistics Clearing House (2002); however, we have no further details about the characteristics of nonparticipating cases due to privacy laws. For selection bias to account for these findings, nonparticipating cases would need to have used aspirin and NSAIDs ~4-fold more often than participating cases, an unlikely explanation. A more likely source of bias might arise if the participating controls differed from the source population with respect to their prevalence of aspirin or NSAID use. Directly comparable data arising from the Australian population are scant; however, the prevalence of aspirin and NSAID use in our sample was similar to that reported in other Australian studies (52, 53). Other factors known to be associated with risks of EAC, notably symptoms of reflux and BMI, were similarly prevalent in our control series to other studies in the Australian population (54, 55). We therefore consider the likelihood of biased selection to be no greater than for previous studies.

Another likely source of error is random misclassification of aspirin, NSAID, or acetaminophen exposure. To assess this, we measured the repeatability of our questionnaire instrument among 85 participants after a mean interval of 4.4 months (56). Good to very good agreement was observed for frequency of intake of aspirin (weighed κ statistic, Kw = 0.53), NSAIDs (Kw = 0.72), and acetaminophen (Kw = 0.58), suggesting that random misclassification is unlikely to be a major source of error.

Our findings are in agreement with the majority of earlier studies. Among those studies that have examined the association between aspirin or NSAID and risk of esophageal cancer, all but two (7, 57) have reported 30% to 50% lower risks of esophageal cancers among people who used NSAIDs compared with never users (44, 45, 58-62). We are aware of only one previous study that has separately measured associations for adenocarcinomas of the esophagus and esophagogastric junction (45). That study reported an inverse association between NSAID

Table 3. Relative risks of esophageal cancers associated with use of aspirin and NSAIDs in the last 5 y, stratified by frequency of reflux symptoms

Frequency of reflux symptoms	Frequency of aspirin	EAC	EGJAC	ESCC
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Never	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Monthly	1.24 (0.70-2.20)	1.22 (0.76-1.94)	1.29 (0.81-2.05)
	<Weekly	1.19 (0.45-3.12)	1.28 (0.62-2.68)	1.29 (0.55-3.03)
	Weekly+	0.96 (0.46-2.00)	0.81 (0.41-1.59)	0.70 (0.36-1.35)
	P_{trend}	0.66	0.45	0.12
<Weekly	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Monthly	0.50 (0.39-0.84)	0.85 (0.55-1.33)	0.81 (0.46-1.45)
	<Weekly	1.86 (1.04-3.13)	0.74 (0.37-1.49)	1.07 (0.46-2.46)
	Weekly+	0.52 (0.26-1.00)	0.76 (0.42-1.35)	0.58 (0.25-1.37)
	P_{trend}	0.31	0.49	0.56
Weekly+	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Monthly	0.40 (0.21-0.73)	0.59 (0.33-1.06)	0.87 (0.41-1.85)
	<Weekly	0.44 (0.18-1.06)	0.72 (0.30-1.69)	1.90 (0.56-6.42)
	Weekly+	0.26 (0.12-0.55)	0.64 (0.33-1.25)	0.72 (0.29-1.78)
	P_{trend}	0.32	0.49	0.82
	$P_{interaction}$	0.01	0.50	0.91
Frequency of reflux symptoms	Frequency of NSAIDs	EAC	EGJAC	ESCC
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Never	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Monthly	1.43 (0.81-2.52)	1.10 (0.67-1.79)	0.99 (0.61-1.59)
	<Weekly	0.87 (0.28-2.67)	1.01 (0.45-2.27)	0.37 (0.11-1.31)
	Weekly+	0.78 (0.35-1.72)	0.78 (0.40-1.51)	0.53 (0.26-1.08)
	P_{trend}	0.19	0.32	0.07
<Weekly	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Monthly	0.63 (0.38-1.04)	0.66 (0.42-1.05)	0.94 (0.53-1.68)
	<Weekly	0.63 (0.31-1.29)	0.40 (0.19-0.87)	0.65 (0.26-1.68)
	Weekly+	1.05 (0.59-1.87)	0.64 (0.36-1.16)	1.06 (0.51-2.21)
	P_{trend}	0.11	0.93	0.77
Weekly+	Never	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	Monthly	0.45 (0.24-0.84)	0.46 (0.25-0.84)	0.60 (0.26-1.40)
	<Weekly	0.47 (0.18-1.26)	0.65 (0.27-1.59)	0.67 (0.20-2.23)
	Weekly+	0.41 (0.21-0.77)	0.32 (0.16-0.62)	0.18 (0.07-0.46)
	P_{trend}	0.60	0.36	0.04
	$P_{interaction}$	0.10	0.06	0.12

NOTE: Adjusted for age (in years), sex, state of residence, household income, cumulative smoking history, mean alcohol consumption, and BMI.

use and risk of both cancers, with slightly greater effects observed for EAC, similar to our study.

We found no evidence that longer durations of exposure to NSAIDs altered the risk of EAC, EGJAC, or ESCC. Of two studies that have assessed the duration of NSAIDs intake and risk of esophageal adenocarcinoma (10, 45), neither observed any association between duration and risk of adenocarcinoma. From five studies that evaluated association between exposure to NSAIDs and risk for any type of esophageal cancer (10, 45, 47, 58-61, 63), three reported lower risks among people with longer exposure to NSAIDs (59, 60, 63). The remaining studies had smaller numbers of participants with wide confidence intervals in the longer duration categories, masking possible associations. We found some evidence that recent use of NSAIDs conferred lower risks of EAC, EGJAC, and ESCC than distant use. Four studies have examined the effects of recency of exposure (10, 44, 45, 61), of which two observed greater reductions in risk associated with more recent use of NSAIDs.

In regard to the specificity of anti-inflammatory medications on EAC risk, all previous studies but one (62) have reported stronger associations with aspirin than NSAIDs. We also found larger reductions in EAC risk associated with aspirin than for other NSAIDs. One possible explanation for this difference in effect could be the stage of involvement of these medications in suppression of the COX pathway, as aspirin blocks this pathway upstream by irreversibly inactivating COX-1 enzyme, whereas other NSAIDs compete with arachidonic acid in binding to COX-1 enzyme. Thus, it is possible that the earlier blockade of the COX pathway may result in stronger risk reduction for cancer.

A particular aim of this investigation was to examine for the possibility that exposure to acid reflux, tobacco smoke, or excess body mass might modify the association between NSAIDs and esophageal cancer. We found consistently stronger risk reductions among those with frequent reflux symptoms, but no difference in associations according to smoking status or BMI. The only other study to have stratified by reflux history did not find stronger effects (45). Our finding might be explained by ''confounding by indication,'' which would occur if people with reflux symptoms avoided using aspirin or NSAIDs out of concern that these medications might exacerbate their symptoms. We found no evidence to support this explanation; indeed, control participants with regular symptoms of reflux were significantly more

Table 4. Relative risks of esophageal cancers associated with measures of NSAID use during the lifetime (interview data)

Measure	EAC	EGJAC	ESCC
Category	OR (95% CI)	OR (95% CI)	OR (95% CI)
Lifetime use of NSAIDs			
Never	1 (Reference)	1 (Reference)	1 (Reference)
Ever	0.40 (0.30-0.54)	0.47 (0.36-0.62)	0.35 (0.25-0.49)
Pattern of intake of NSAIDs			
Never	1 (Reference)	1 (Reference)	1 (Reference)
Occasional	0.49 (0.33-0.71)	0.64 (0.46-0.88)	0.53 (0.36-0.78)
Regular	0.34 (0.23-0.49)	0.35 (0.25-0.49)	0.21 (0.13-0.33)
P	<0.01	<0.01	<0.01
Recency of intake of NSAIDs			
Never	1 (Reference)	1 (Reference)	1 (Reference)
>5 y ago	0.54 (0.31-0.91)	0.62 (0.38-1.01)	0.48 (0.26-0.89)
1-5 y ago	0.37 (0.27-0.51)	0.45 (0.33-0.59)	0.33 (0.23-0.47)
P	<0.01	<0.01	<0.01
Duration of intake of NSAIDs			
Never	1 (Reference)	1 (Reference)	1 (Reference)
≤5 y	0.38 (0.27-0.55)	0.53 (0.39-0.72)	0.38 (0.26-0.55)
>5 y	0.42 (0.29-0.61)	0.40 (0.28-0.58)	0.32 (0.21-0.49)
P	<0.01	<0.01	<0.01
Regularity and duration			
Never	1 (Reference)	1 (Reference)	1 (Reference)
Occasional <5 y	0.47 (0.29-0.77)	0.70 (0.47-1.05)	0.66 (0.41-1.05)
Occasional ≥5 y	0.47 (0.30-0.74)	0.50 (0.33-0.76)	0.36 (0.21-0.61)
Regular <5 y	0.29 (0.18-0.48)	0.44 (0.29-0.66)	0.20 (0.11-0.36)
Regular ≥5 y	0.38 (0.23-0.62)	0.25 (0.14-0.43)	0.26 (0.14-0.47)
P_{trend}	<0.01	<0.01	<0.01

NOTE: Adjusted for age (in years), sex, state of residence, household income, cumulative smoking history, mean alcohol consumption, BMI, and frequency of gastroesophageal reflux symptoms 10 y before diagnosis.

likely to use aspirin or NSAIDs than controls who did not experience reflux. Similar findings have been observed elsewhere (10, 45). Alternatively, the stronger effect observed among people with reflux could reflect a biological mechanism. Gastroesophageal acid reflux is held to increase the risk of esophageal adenocarcinoma through a pathway of chronic inflammation and repair. Aspirin and NSAIDs suppress the COX and lipoxygenase pathways, which, in turn, leads to inhibition of prostaglandin synthesis, reducing prostaglandin and 15-lipoxygenase–induced immunosuppression and apoptosis (64-66). Thus, a plausible explanation for the association might be that people with the greatest ''inflammatory burden'' in the distal esophagus (that is, those with frequent symptoms of acid reflux) experience greater reductions in risks of EAC than people without inflammation because of the specificity of aspirin and NSAIDs for inhibiting the inflammatory pathways. Although our findings for aspirin support this explanation, the associations with NSAIDs among the frequent reflux group were not specific for EAC, being also observed for EGJAC and ESCC.

In summary, we have found significant reductions in risk of EAC, EGJAC, and ESCC associated with frequent use of aspirin and NSAIDs, but not acetaminophen. Use of aspirin and NSAIDs was associated with substantially lower risks of esophageal adenocarcinoma among people with frequent symptoms of reflux, but not among people who did not experience reflux symptoms. Although these findings are consistent with, and extend, previous reports from observational studies about the role of NSAIDs in inhibiting esophageal carcinogenesis, definitive evidence of benefit from these medications awaits the findings of randomized trials (24).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Appendix A. The Australian Cancer Study: Esophageal Cancer

Investigators: David C. Whiteman, MBBS, Ph.D.; Penelope M. Webb, M.A., Ph.D.; Adele C. Green, MBBS, Ph.D.; Nicholas K. Hayward, Ph.D.; Peter G. Parsons, Ph.D.; David M. Purdie, Ph.D.

Clinical collaborators: B. Mark Smithers, FRACS; David Gotley, FRACS, Ph.D.; Andrew Clouston, FRCPA, Ph.D.; Ian Brown, FRCPA.

Project Manager: Suzanne Moore, RN, MPH.

Database: Karen Harrap, BIT; Troy Sadkowski, BIT.

Research Nurses: Suzanne O'Brien, RN, MPH; Ellen Minehan, RN; Deborah Roffe, RN; Sue O'Keefe, RN; Suzanne Lipshut, RN; Gabby Connor, RN; Hayley Berry, RN; Frances Walker, RN; Teresa Barnes, RN; Janine Thomas, RN; Linda Terry, RN, MPH; Michael Connard, B.Sc., Leanne Bowes, B.Sc.; MaryRose Malt, RN; Jo White, RN.

Clinical Contributors:

Australian Capital Territory: Charles Mosse, FRACS; Noel Tait, FRACS.

New South Wales: Chris Bambach, FRACS; Andrew Biankan, FRACS; Roy Brancatisano, FRACS; Max Coleman, FRACS; Michael Cox, FRACS; Stephen Deane, FRACS; Gregory L. Falk, FRACS; James Gallagher, FRACS; Mike Hollands, FRACS; Tom Hugh, FRACS; David Hunt, FRACS; John Jorgensen, FRACS; Christopher Martin, FRACS; Mark Richardson, FRACS; Garrett Smith, FRACS; Ross Smith, FRACS; David Storey, FRACS.

Queensland: John Avramovic, FRACS; John Croese, FRACP; Justin D'Arcy, FRACS; Stephen Fairley, FRACP; John Hansen, FRACS; John Masson, FRACP; Les Nathanson, FRACS; Barry O'Loughlin, FRACS; Leigh Rutherford, FRACS; Richard Turner, FRACS; Morgan Windsor, FRACS.
South Australia: Justin Bessell, FRACS; Peter Devitt, FRACS; Glyn Jamieson, FRACS; David Watson, FRACS.
Victoria: Stephen Blamey, FRACS; Alex Boussioutas, FRACP; Richard Cade, FRACS; Gary Crosthwaite, FRACS; Ian Faragher, FRACS; John Gribbin, FRACS; Geoff Hebbard, FRACP; George Kiroff, FRACS; Bruce Mann, FRACS; Bob Millar, FRACS; Paul O'Brien, FRACS; Robert Thomas, FRACS; Simon Wood, FRACS.
Western Australia: Steve Archer, FRACS; Kingsley Faulkner, FRACS; Jeff Hamdorf, FRACS.

Acknowledgments

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
We thank Harish Babu, M.D., for his assistance with pathology abstractions.

References

1. Adami HO, Trichopoulos D. Obesity and mortality from cancer. N Engl J Med 2003;348:1623–4.
2. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 2005;97:142–6.
3. Montesano R, Hainaut P. Molecular precursor lesions in oesophageal cancer. Cancer Surv 1998;32:53–68.
4. Omundsen M, Babor R, Johnston P. Outcomes after oesophagogastrectomy for carcinoma of the oesophagus. ANZ J Surg 2007;77:37–9.
5. Zhang X, Watson DI, Jamieson GG, Lally C, Bessell JR, Devitt PG. Outcome of oesophagectomy for adenocarcinoma of the oesophagus and oesophagogastric junction. ANZ J Surg 2005;75:513–9.
6. Engel LS, Chow WH, Vaughan TL, et al. Population attributable risks of esophageal and gastric cancers. J Natl Cancer Inst 2003;95:1404–13.
7. Garidou A. Life-style factros and medical conditions in relation to esophageal cancer by histologic type in a low-risk population. Int J Cancer 1996;68:295–99.
8. Gammon MD, Terry MB, Arber N, et al. Nonsteroidal anti-inflammatory drug use associated with reduced incidence of adenocarcinomas of the esophagus and gastric cardia that over-express cyclin D1: a population-based study. Cancer Epidemiol Biomarkers Prev 2004;13:34–9.
9. Vaughan TL, Davis S, Kristal A, Thomas DB. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 1995;4:85–92.
10. Farrow DC, Vaughan TL, Hansten PD, et al. Use of aspirin and other nonsteroidal anti-inflammatory drugs and risk of esophageal and gastric cancer. Cancer Epidemiol Biomarkers Prev 1998;7:97–102.
11. Yokoyama A, Omori T, Yokoyama T, et al. Risk of squamous cell carcinoma of the upper aerodigestive tract in cancer-free alcoholic Japanese men: an endoscopic follow-up study. Cancer Epidemiol Biomarkers Prev 2006;15:2209–15.
12. Allen JW, Richardson JD, Edwards MJ. Squamous cell carcinoma of the esophagus: a review and update. Surg Oncol 1997;6:193–200.
13. Cheng KK, Day NE. Nutrition and esophageal cancer. Cancer Causes Control 1996;7:33–40.
14. Messmann H. Squamous cell cancer of the oesophagus. Best Pract Res Clin Gastroenterol 2001;15:249–65.
15. Valsecchi MG. Modelling the relative risk of esophageal cancer in a case-control study. J Clin Epidemiol 1992;45:347–55.
16. Hashibe M, Boffetta P, Janout V, et al. Esophageal cancer in Central and Eastern Europe: tobacco and alcohol. Int J Cancer 2007;120:1518–22.
17. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340:825–31.
18. Wu AH, Wan P, Bernstein L. A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus (United States). Cancer Causes Control 2001;12:721–32.
19. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer 2004;4:579–91.
20. Brown LM, Swanson CA, Gridley G, et al. Adenocarcinoma of the esophagus: role of obesity and diet. J Natl Cancer Inst 1995;87:104–9.
21. Chow WH, Blot WJ, Vaughan TL, et al. Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 1998;90:150–5.
22. Lagergren J, Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. Ann Intern Med 1999;130:883–90.
23. Whiteman DC, Sadeghi S, Pandeya N, et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. Gut 2007.
24. Jankowski J, Barr H. Improving surveillance for Barrett's oesophagus: AspECT and BOSS trials provide an evidence base. BMJ 2006;332:1512.
25. Buskens CJ, Van Rees BP, Sivula A, et al. Prognostic significance of elevated cyclooxygenase 2 expression in patients with adenocarcinoma of the esophagus. Gastroenterology 2002;122:1800–7.
26. Cheong E, Igali L, Harvey I, et al. Cyclo-oxygenase-2 expression in Barrett's oesophageal carcinogenesis: an immunohistochemical study. Aliment Pharmacol Ther 2003;17:379–86.
27. Zhang W, Wang L, Chang A, Jin Y, Rao J. Immunohistochemical analysis of cyclooxygenase-2 expression in premalignant and malignant esophageal glandular and squamous lesions in Cixian, China. Cancer Detect Prev 2003;27:243–9.
28. Yu HP, Xu SQ, Liu L, et al. Cyclooxygenase-2 expression in squamous dysplasia and squamous cell carcinoma of the esophagus. Cancer Lett 2003;198:193–201.
29. Kuo KT, Chow KC, Wu YC, et al. Clinicopathologic significance of cyclooxygenase-2 overexpression in esophageal squamous cell carcinoma. Ann Thorac Surg 2003;76:909–14.
30. Zimmermann KC, Sarbia M, Weber AA, Borchard F, Gabbert HE, Schror K. Cyclooxygenase-2 expression in human esophageal carcinoma. Cancer Res 1999;59:198–204.
31. Wang LS, Chow KC, Wu YC. Effects of platelet activating factor, butyrate and interleukin-6 on cyclooxygenase-2 expression in human esophageal cancer cells. Scand J Gastroenterol 2002;37:467–75.
32. Lagorce C, Paraf F, Vidaud D, et al. Cyclooxygenase-2 is expressed frequently and early in Barrett's oesophagus and associated adenocarcinoma. Histopathology 2003;42:457–65.
33. Morris CD, Armstrong GR, Bigley G, Green H, Attwood SE. Cyclooxygenase-2 expression in the Barrett's metaplasia-dysplasia-adenocarcinoma sequence. Am J Gastroenterol 2001;96:990–6.
34. Kandil HM, Tanner G, Smalley W, Halter S, Radhika A, Dubois RN. Cyclooxygenase-2 expression in Barrett's esophagus. Dig Dis Sci 2001;46:785–9.
35. Shamma A, Yamamoto H, Doki Y, et al. Up-regulation of cyclooxygenase-2 in squamous carcinogenesis of the esophagus. Clin Cancer Res 2000;6:1229–38.
36. Shirvani VN, Ouatu-Lascar R, Kaur BS, Omary MB, Triadafilopoulos G. Cyclooxygenase 2 expression in Barrett's esophagus and adenocarcinoma: *Ex vivo* induction by bile salts and acid exposure. Gastroenterology 2000;118:487–96.
37. Abdalla SI, Lao-Sirieix P, Novelli MR, Lovat LB, Sanderson IR, Fitzgerald RC. Gastrin-induced cyclooxygenase-2 expression in Barrett's carcinogenesis. Clin Cancer Res 2004;10:4784–92.
38. Tsujii M, Kawano S, DuBois RN. Cyclooxygenase-2 expression in human colon cancer cells increases metastatic potential. Proc Natl Acad Sci U S A 1997;94:3336–40.
39. Marrogi AJ, Travis WD, Welsh JA, et al. Nitric oxide synthase, cyclooxygenase 2, and vascular endothelial growth factor in the angiogenesis of non-small cell lung carcinoma. Clin Cancer Res 2000;6:4739–44.
40. Gately S. The contributions of cyclooxygenase-2 to tumor angiogenesis. Cancer Metastasis Rev 2000;19:19–27.
41. Rubio CA. Further studies on the therapeutic effect of indomethacin on esophageal tumors. Cancer 1986;58:1029–31.
42. Rubio CA. Antitumoral activity of indomethacin on experimental esophageal tumors. J Natl Cancer Inst 1984;72:705–7.
43. Marnett LJ. Aspirin and the potential role of prostaglandins in colon cancer. Cancer Res 1992;52:5575–89.
44. Langman MJ, Cheng KK, Gilman EA, Lancashire RJ. Effect of anti-inflammatory drugs on overall risk of common cancer: case-control study in general practice research database. BMJ 2000;320:1642–6.

45. Anderson LA, Johnston BT, Watson RG, et al. Nonsteroidal anti-inflammatory drugs and the esophageal inflammation-metaplasia-adenocarcinoma sequence. Cancer Res 2006;66:4975–82.
46. Corley DA, Kerlikowske K, Verma R, Buffler P. Protective association of aspirin/NSAIDs and esophageal cancer: a systematic review and meta-analysis. Gastroenterology 2003;124:47–56.
47. Vaughan TL, Dong LM, Blount PL, et al. Non-steroidal anti-inflammatory drugs and risk of neoplastic progression in Barrett's oesophagus: a prospective study. Lancet Oncol 2005;6:945–52.
48. Olsen CM, Bain CJ, Jordan SJ, et al. Recreational physical activity and epithelial ovarian cancer: a case-control study, systematic review, and meta-analysis. Cancer Epidemiol Biomarkers Prev 2007;16:2321–30.
49. Hamilton SR, Aaltonen LA; International Agency for Research on Cancer; and World Health Organization. Pathology and genetics of tumours of the digestive system. World Health Organization classification of tumours. Lyon: IARC Press. 2000. p. 314.
50. Murray L, Watson P, Johnston B, Sloan J, Mainie IM, Gavin A. Risk of adenocarcinoma in Barrett's oesophagus: population based study. BMJ 2003;327:534–5.
51. Hampel H, Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. Ann Intern Med 2005;143:199–211.
52. Butler GJ, Neale R, Green AC, Pandeya N, Whiteman DC. Nonsteroidal anti-inflammatory drugs and the risk of actinic keratoses and squamous cell cancers of the skin. J Am Acad Dermatol 2005;53:966–72.
53. Wang JJ, Mitchell P, Smith W, Gillies M, Billson F. Systemic use of anti-inflammatory medications and age-related maculopathy: the Blue Mountains Eye Study. Ophthalmic Epidemiol 2003;10:37–48.
54. Talley NJ, Quan C, Jones MP, Horowitz M. Association of upper and lower gastrointestinal tract symptoms with body mass index in an Australian cohort. Neurogastroenterol Motil 2004;16:413–9.
55. Australian Bureau of Statistics. National Health Survey: summary of results 2004-05. In: STATISTICS ABO, editor; 2006, Commonwealth of Australia.
56. Karatela S, Purdie DM, Green AC, Webb PM, Whiteman DC. Repeatability of self-reported information for population-based studies of cancer. Asian Pac J Cancer Prev 2006;7:303–8.
57. Cheng KK, Sharp L, McKinney PA, et al. A case-control study of oesophageal adenocarcinoma in women: a preventable disease. Br J Cancer 2000;83:127–32.
58. Jayaprakash V, Menezes RJ, Javle MM, et al. Regular aspirin use and esophageal cancer risk. Int J Cancer 2006;119:202–7.
59. Suleiman UL, Harrison M, Britton A, McPherson K, Bates T. H2-receptor antagonists may increase the risk of cardio-oesophageal adenocarcinoma: a case-control study. Eur J Cancer Prev 2000;9:185–91.
60. Thun MJ, Namboodiri MM, Calle EE, Flanders WD, Heath CW, Jr. Aspirin use and risk of fatal cancer. Cancer Res 1993;53:1322–7.
61. Vaughan TL, Kristal AR, Blount PL, et al. Nonsteroidal anti-inflammatory drug use, body mass index, and anthropometry in relation to genetic and flow cytometric abnormalities in Barrett's esophagus. Cancer Epidemiol Biomarkers Prev 2002;11:745–52.
62. Ranka S, Gee JM, Johnson IT, Skinner J, Hart AR, Rhodes M. Non-steroidal anti-inflammatory drugs, lower oesophageal sphincter-relaxing drugs and oesophageal cancer. A case-control study. Digestion 2006;74:109–15.
63. Coogan PF, Rosenberg L, Palmer JR, et al. Nonsteroidal anti-inflammatory drugs and risk of digestive cancers at sites other than the large bowel. Cancer Epidemiol Biomarkers Prev 2000;9:119–23.
64. Berkel H, Holcombe RF, Middlebrooks M, Kannan K. Nonsteroidal antiinflammatory drugs and colorectal cancer. Epidemiol Rev 1996;18:205–17.
65. Morgan G. Non-steroidal anti-inflammatory drugs and the chemoprevention of colorectal and oesophageal cancers. Gut 1996;38:646–8.
66. Shureiqi I, Chen D, Lotan R, et al. 15-Lipoxygenase-1 mediates nonsteroidal anti-inflammatory drug-induced apoptosis independently of cyclooxygenase-2 in colon cancer cells. Cancer Res 2000;60:6846–50.

American Journal of Epidemiology
Vol. 168, No. 1
DOI: 10.1093/aje/kwn091
Advance Access publication May 15, 2008

Practice of Epidemiology

Associations of Duration, Intensity, and Quantity of Smoking with Adenocarcinoma and Squamous Cell Carcinoma of the Esophagus

Nirmala Pandeya[1,2], Gail M. Williams[2], Shahram Sadhegi[1,2], Adèle C. Green[1], Penelope M. Webb[1], and David C. Whiteman[1]

[1] Population Studies and Human Genetics Division, Queensland Institute of Medical Research, Herston, Queensland, Australia.
[2] School of Population Health, University of Queensland, Brisbane, Queensland, Australia.

Received for publication December 12, 2007; accepted for publication March 18, 2008.

Smoking has been identified as a risk factor for esophageal cancer; however, there is evidence that magnitudes and patterns of association differ by histologic type. The authors aimed to measure and compare the independent effects of various dimensions of smoking (duration, intensity, total dose, and time since quitting) on risks of esophageal adenocarcinoma (EAC), gastroesophageal junction adenocarcinoma (GEJAC), and esophageal squamous cell carcinoma (ESCC). They used data from a population-based Australian case-control study (2002–2005) comprising 367 EAC cases, 426 GEJAC cases, and 309 ESCC cases and 1,580 controls. Multivariate logistic and generalized additive logistic regression (for nonlinear dose effects) were used. Ever smokers had significantly higher risks of EAC (odds ratio (OR) = 1.7, 95% confidence interval (CI): 1.3, 2.3), GEJAC (OR = 2.4, 95% CI: 1.8, 3.2), and ESCC (OR = 2.8, 95% CI: 2.0, 4.0) than did never smokers; however, there were significant differences in magnitude and patterns of association between subtypes. When multiple dimensions of smoking were assessed concurrently, duration was significantly associated with all three subtypes but intensity was associated only with GEJAC and ESCC, and the associations were nonlinear. For all types of esophageal cancer, time since quitting was independently associated with approximately 15–19% risk reductions per decade.

esophageal neoplasms; smoking

Abbreviations: CI, confidence interval; EAC, esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma; GEJAC, gastroesophageal junction adenocarcinoma; OR, odds ratio.

Tobacco smoking is an established risk factor for both of the common histologic types of esophageal cancer; however, there is evidence that the patterns of risk differ for each (1–3). Thus, while most epidemiologic studies of esophageal squamous cell carcinoma (ESCC) have reported monotonic risk increases with increasing levels of smoking (1–5), studies of esophageal adenocarcinoma (EAC) and gastroesophageal junction adenocarcinoma (GEJAC) have typically reported associations of smaller magnitude (3, 6–8). Such findings suggest that smoking may cause different types of esophageal cancer through different mechanisms.

Past exposure to tobacco smoke is typically measured across dimensions such as duration, intensity, cumulative dose, and time since quitting (among ex-smokers). Each dimension can be assessed independently as a risk factor for esophageal cancer. Studies investigating the role of smoking in cancer at other sites (notably the lung) have shown that different dimensions of smoking may have independent or joint associations with cancer, depending upon the histologic subtype(s) under consideration. In addition to the potential for deriving mechanistic insights, assessing the role of the various components of smoking exposure in cancer risk is necessary for estimating the likely impact of

Correspondence to Dr. David Whiteman, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Brisbane, Queensland 4029, Australia (e-mail: david.whiteman@qimr.edu.au).

smoking control strategies and optimizing evidence-based health advice. While investigators have previously reported on the risks of esophageal cancer associated with smoking (2, 3, 8–10), none (to our knowledge) have assessed the independent contribution of each dimension of smoking to determine which, if any, is of primary importance.

We analyzed the effects of multiple dimensions of smoking exposure on esophageal cancer risk using approaches similar to those developed to investigate the causes of lung cancer (4, 11, 12). Specifically, we sought to quantify the independent associations between dimensions of smoking and their dose patterns and the risks of esophageal and gastroesophageal cancer and to explore possible subtype-specific differences in these associations.

MATERIALS AND METHODS

Study design and participants

We conducted a population based case-control study of esophageal cancer. Full details on the study design and recruitment have been published previously (13). Briefly, eligible case patients were people aged 18–79 years with a histologically confirmed primary invasive cancer of the esophagus or gastroesophageal junction diagnosed between July 1, 2002 (July 1, 2001, in Queensland) and June 30, 2005, in mainland states of Australia. Patients were recruited through either major treatment centers or state-based cancer registries. Through treatment centers, we identified 1,610 eligible patients; of these, 167 died before consent could be obtained, the treating doctor denied permission to contact 71, and 181 were excluded (91 were too ill, 41 were unable to communicate in English, 23 were mentally incapable, and 26 could not be contacted). Through the cancer registries, of 739 eligible patients who were alive at the time of identification, the treating doctor denied permission to contact 84, 37 were either physically or mentally incapable of participating, and 232 could not be contacted. (A further 835 persons with registry notification of ''esophageal cancer'' had died before study identification, and their records could not be verified.) Of the 1,577 patients with esophageal cancer invited to participate in the study (1,191 through clinics and 386 through cancer registries), 1,102 patients returned a completed questionnaire (70 percent of all patients invited; 35 percent of all living and deceased persons in mainland Australia who had been diagnosed with incident esophageal cancer). Final numbers of case participants, by histologic type, were: EAC, 367; GEJAC, 426; and ESCC, 309.

Potential controls were randomly selected from the Australian electoral roll by 5-year age group and state of residence to match the distribution of the case series. We aimed for similar numbers of male cases and controls in each stratum of age and state; female controls were intentionally oversampled at all ages to accommodate their simultaneous enrollment in a case-control study of ovarian cancer (14). Of 3,258 potentially eligible control participants who were invited to participate, 175 were excluded because they were deceased ($n = 16$), too ill ($n = 61$), or unable to communicate in English ($n = 98$), and 41 were lost to follow-up between initial contact and participation. Of the 3,042 remaining controls, 1,680 (55 percent) accepted. Completed questionnaires were returned by 1,580 controls (49 percent of all potentially eligible controls).

Data collection

Health and lifestyle factors. Participants self-completed a health and lifestyle questionnaire asking about their education, height, and weight 1 year prior (1 year before diagnosis for cases). We calculated body mass index by dividing weight (kg) by height (m) squared and used standard categories for analysis (healthy weight: <25.0; overweight: 25.0–29.9; obese: ≥30). Participants were also asked about their past alcohol consumption, frequency of heartburn (''a burning pain behind the breastbone after eating'') or acid reflux (''a sour taste from acid or bile rising up into the mouth or throat''), and aspirin use in the past 5 years.

Smoking history. Participants were asked whether, over their whole life, they had ever smoked more than 100 cigarettes or cigars (or equivalent use of pipes). Positive responses led to further questions about the age at which they started smoking, the age at which they stopped smoking permanently (among ex-smokers), the amount they smoked in a typical day, the number of days per week that they smoked, and the number of years they had smoked. We asked participants to report the duration of each episode of temporarily stopping smoking for more than 6 months and their age at the time. In addition, participants were asked to estimate the average number of cigarettes, cigars, or pipes smoked per day during each decade of life.

Derivation of smoking variables. Current smokers and ex-smokers were defined by their smoking status at 1 year prior to their reference age (age at diagnosis for cases, age at study participation for controls). Smoking duration was defined as the difference between starting age and either permanent quitting age (ex-smokers) or reference age (current smokers), after subtracting the cumulative duration of any episodes of temporarily quitting smoking. Smoking intensity was defined as the average number of cigarettes smoked in a typical day.

We estimated each participant's lifetime cumulative quantity of tobacco smoked (dose) in pack-years, using two algorithms. We used a simple algorithm to calculate the product of smoking duration and intensity. We used a detailed algorithm to calculate the sum of decade-specific smoking doses, where each decade-specific smoking dose was the product of the smoking intensity during that decade, the number of days of smoking per week, and smoking duration within that decade. The correlation between doses calculated by means of the two algorithms was very high (Pearson correlation = 0.95); however, the detailed algorithm resulted in significantly lower dose estimates (~2 pack-years). For these analyses, we used the cumulative smoking dose calculated by means of the detailed algorithm.

Time since quitting was calculated as the difference between the age at which ex-smokers had permanently stopped smoking and their age 1 year prior to their reference age. For categorical data analysis, each of the continuous smoking measures so derived was categorized at approximate quartile cutpoints from the control distribution.

Statistical methods

In the analyses, we aimed to quantify the associations between key measures of smoking exposure (duration, intensity, dose, and time since quitting) and the risks of EAC, GEJAC, and ESCC. In particular, we sought to estimate the independent effect of each dimension of smoking after also considering the effects of the other smoking dimensions. Our approach was first to fit standard logistic models using single measures of smoking separately, adjusted for the potentially confounding effects of nonsmoking factors, similar to previous studies that investigated smoking and esophageal cancer (2, 3, 8–10). We then fitted more complex models in which multiple smoking measures were modeled simultaneously to assess which of the measures, if any, were most strongly associated with cancer risk (11, 15). Finally, we assessed the effect of smoking cessation on cancer risk by adding the term "time since quitting" to models containing other dimensions of smoking exposure.

Risk estimates for individual smoking measures. For single smoking measures, we used multivariate logistic regression (GENMOD procedure) in SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina) to calculate odds ratios and 95 percent confidence intervals, using never smokers as the reference category. Statistical significance was determined using a two-sided test at $\alpha = 0.05$. Trend tests for ordinal categorical variables were performed using median values for each category as continuous values in the model and were restricted to exposed groups only. We adjusted for the matching variables (sex, age) as well as educational level, average weekly alcohol consumption, body mass index, aspirin use, and frequency of heartburn or reflux 10 years prior to participation.

Risk estimates for qualitative and individual quantitative smoking measures. In the next step, we sought to simultaneously measure the qualitative effect of smoking and the dose effect for each dimension. We fitted a series of models which included a smoking indicator term (never, ever) as well as a separate term for each specific dimension of smoking. To allow the model to simultaneously estimate risks of smoking overall, together with risks for each dimension, we transformed the continuous measures by subtracting their respective mean values from the original values among smokers and allocating a value of zero for never smokers (a transformation known as "centering") (11, 16). Thus, the transformed continuous variables had a value of zero for both never smokers and "average" smokers; for all other smokers, the value of the transformed variable was the deviation from the mean. The indicator variable was estimated at the same value (zero) for both never smokers and average smokers; the dose effect was estimated from smokers only and depended on the extent to which their risk varied linearly (on the logit scale) with their increment in smoking above or below the mean. Thus, when interpreting risk estimates from these models, it is important to recognize that the reference value is the mean for the dimension of smoking being assessed.

Risk estimates for qualitative and multiple simultaneous quantitative smoking measures. In the final model, we added other continuous smoking variables to quantify the dose-response for each dimension of smoking while adjusting for the others. The model-building strategy was based on Akaike's information criterion; models with minimum Akaike values were considered the best fit for each outcome.

All regression analyses were performed on participants with complete data for smoking and other confounding factors so that Akaike's information criterion was comparable across the nested (or nonnested) models. Altogether, 121 participants (46 controls, 21 cases with EAC, 22 cases with GEJAC, and 32 cases with ESCC) were excluded from the analysis because of missing data. Among those, 89 had data on smoking (30 percent nonsmokers, 44 percent ex-smokers, and 26 percent current smokers).

In the risk factor models for each outcome, we checked for nonlinearity in the dose effect of continuous smoking variables by means of generalized additive logistic models (17), using R software (CRAN package mgcv) (18, 19). Cubic splines fixed at 3 degrees of freedom (df) were used to test for nonlinear effects; nonlinear terms were retained only if they significantly improved model fit (17).

RESULTS

Risk estimates for individual smoking measures

Table 1 presents the risk estimates for EAC, GEJAC, and ESCC for each dimension of smoking fitted as a categorical variable, adjusted for other nonsmoking confounding variables. Risk estimates for smoking measures were modestly attenuated after adjustment for confounding variables (particularly acid reflux and body mass index for EAC and GEJAC and alcohol for ESCC) (data not shown). Compared with never smokers, current smokers had significantly increased risks of ESCC and GEJAC and a greater than twofold elevation in risk for EAC. Ex-smokers had more than a twofold increased risk of ESCC and significant 40–70 percent elevations for GEJAC and EAC. We found no association with age at starting smoking for any type of esophageal cancer; however, the range was limited. Longer durations of smoking were more strongly associated with cancer than shorter durations; significantly increased risks were observed for smoking durations greater than 25 years for EAC, for durations greater than 15 years for GEJAC, and for all durations for ESCC. There was no significant linear trend in the risk of EAC or GEJAC with increasing smoking intensity, whereas a significant trend was observed with increasing smoking intensity for ESCC. Total cumulative dose was also significantly associated with all subtypes, with generally higher risks being observed for ESCC than for EAC and GEJAC for a given category.

We assessed the effect of smoking cessation by comparing the risks of cancer between ex-smokers and never smokers. In this analysis, risks of EAC among ex-smokers remained significantly elevated until 20 years postcessation; for GEJAC and ESCC, risks among ex-smokers remained elevated for up to 30 years.

Effects of smoking duration, intensity, and cumulative dose

When we estimated the risks of cancer associated with incremental changes in each dimension of smoking

TABLE 1. Odds ratios for different histologic types of esophageal cancer according to various dimensions of tobacco smoking in a simple categorical analysis, Australia, 2002–2005

Variable*	No. of controls	Esophageal adenocarcinoma ($n = 367$)			Gastroesophageal junction adenocarcinoma ($n = 426$)			Esophageal squamous cell carcinoma ($n = 309$)		
		No. of cases	OR†,‡	95% CI†	No. of cases	OR‡	95% CI	No. of cases	OR‡	95% CI
Smoking status										
Never smoker§	710	93	1.00		97	1.00		78	1.00	
Ex-smoker	639	198	1.46	1.05, 2.02	210	1.75	1.28, 2.38	133	2.18	1.51, 3.17
Current smoker	208	73	2.51	1.66, 3.82	116	4.25	2.97, 6.09	94	4.58	2.99, 7.02
p value				<0.001			<0.001			<0.001
Age (years) at starting smoking										
<15	192	77	1.57	1.04, 2.39	80	2.08	1.40, 3.07	54	2.79	1.72, 4.52
15–16	242	72	1.60	1.07, 2.38	96	2.29	1.59, 3.31	58	2.86	1.82, 4.49
17–18	212	61	1.56	1.02, 2.39	73	2.20	1.50, 3.22	57	2.45	1.55, 3.88
>18	199	61	2.01	1.31, 3.08	77	2.71	1.86, 3.97	58	3.20	2.05, 5.00
p-trend				0.44			0.23			0.53
Duration (years) of smoking										
≤15	229	41	1.29	0.82, 2.03	46	1.47	0.97, 2.25	32	1.97	1.20, 3.25
15.01–25	205	47	1.43	0.91, 2.23	77	2.43	1.65, 3.57	33	2.27	1.37, 3.77
25.01–35	207	77	1.73	1.16, 2.59	86	2.51	1.72, 3.65	52	2.45	1.54, 3.90
>35	227	108	2.22	1.50, 3.29	120	2.96	2.06, 4.27	111	4.25	2.80, 6.46
p-trend				0.01			0.002			<0.001
Intensity of smoking (cigarettes/day)										
0–9	184	22	0.88	0.51, 1.51	37	1.45	0.92, 2.28	27	1.44	0.83, 2.48
10–19	227	84	2.12	1.44, 3.14	69	2.04	1.39, 3.00	55	2.62	1.67, 4.13
20–25	292	93	1.69	1.15, 2.47	152	3.22	2.30, 4.50	79	3.24	2.11, 4.99
>25	165	74	1.89	1.23, 2.90	71	2.15	1.42, 3.26	65	4.71	2.92, 7.60
p value				0.12			0.13			<0.001
Cumulative dose (pack-years)										
≤10	294	47	1.14	0.75, 1.75	55	1.38	0.93, 2.05	43	1.60	1.00, 2.56
10.01–20	172	50	1.69	1.08, 2.65	63	2.42	1.61, 3.65	28	2.10	1.21, 3.63
20.01–30	135	45	1.62	1.00, 2.61	62	2.95	1.95, 4.48	44	4.62	2.84, 7.51
>30	267	131	2.26	1.56, 3.28	149	3.04	2.15, 4.31	112	3.93	2.58, 5.99
p-trend				0.003			<0.001			<0.001
Time (years) since quitting smoking										
≤10 (ex-smokers only)	146	49	1.58	1.00, 2.51	42	1.59	1.01, 2.51	36	2.39	1.42, 4.01
10.01–20	156	67	1.99	1.29, 3.06	65	2.16	1.42, 3.28	38	2.94	1.77, 4.89
20.01–30	174	47	1.26	0.79, 1.99	61	1.95	1.30, 2.94	35	2.20	1.32, 3.66
>30	163	35	1.06	0.65, 1.73	42	1.30	0.83, 2.06	24	1.44	0.82, 2.52
p-trend				0.003			<0.001			<0.001

* Categories were based on the approximate quartile values among the controls.

† OR, odds ratio; CI, confidence interval.

‡ Adjusted for age, sex, education, frequency of aspirin use, average alcohol intake, body mass index in the past year, and frequency of heartburn or acid reflux. Trend tests were performed using median values for each category and excluded never smokers.

§ Never smokers were the reference category for all analyses.

modeled simultaneously with an indicator variable (ever/never smoker), the highest risks for each type of cancer were observed with the qualitative dimension ''ever smoking'' (table 2). The odds of ever smoking were elevated approximately 70 percent for EAC, 130 percent for GEJAC, and 180 percent for ESCC, regardless of which other dimensions of smoking were included in the model. After partitioning of the qualitative effect of ever smoking, risks

TABLE 2. Odds ratios for different histologic types of esophageal cancer according to various dimensions of tobacco smoking in simultaneous modeling of qualitative and individual quantitative smoking measures, Australia, 2002–2005

Model*	Esophageal adenocarcinoma			Gastroesophageal junction adenocarcinoma			Esophageal squamous cell carcinoma		
	OR†,‡	95% CI†	*p* value	OR‡	95% CI	*p* value	OR‡	95% CI	*p* value
Ever smoking	1.71	1.25, 2.33	<0.001	2.38	1.78, 3.18	<0.001	2.79	1.97, 3.95	<0.001
Duration of smoking (per 10 years)	1.18	1.05, 1.34	0.007	1.19	1.07, 1.32	0.002	1.21	1.06, 1.37	0.004
Ever smoking	1.67	1.23, 2.28	0.001	2.33	1.74, 3.11	<0.001	2.85	2.01, 4.05	<0.001
Intensity of smoking (per 10 cigarettes/day)	1.02	0.91, 1.14	0.75	1.04	0.93, 1.15	0.49	1.20	1.07, 1.35	0.002
Ever smoking	1.69	1.24, 2.31	<0.001	2.36	1.77, 3.15	<0.001	2.85	2.01, 4.04	<0.001
Cumulative dose (per 10 pack-years)	1.06	0.99, 1.14	0.08	1.06	1.00, 1.13	0.06	1.11	1.04, 1.19	0.003
Ever smoking	1.64	1.21, 2.22	0.002	2.27	1.70, 3.02	<0.001	2.79	1.97, 3.97	<0.001
Age at starting smoking (per 5 years)	1.11	0.91, 1.37	0.30	1.16	0.98, 1.37	0.09	0.96	0.78, 1.18	0.69
Ever smoking	1.70	1.25, 2.32	<0.001	2.32	1.74, 3.10	<0.001	2.75	1.94, 3.90	<0.001
Time since quitting smoking (per 10 years)	0.81	0.72, 0.92	0.001	0.79	0.71, 0.89	<0.001	0.80	0.70, 0.91	<0.001

* All continuous smoking measures were centered (by subtracting the mean value from the original value among smokers), and estimates of odds ratios were obtained using separate models that each included an indicator variable for ever/never smoking.

† OR, odds ratio; CI, confidence interval.

‡ Adjusted for age, sex, education, frequency of aspirin use, average alcohol intake, body mass index in the past year, and frequency of heartburn or acid reflux.

for all types of esophageal cancer increased significantly with longer durations of smoking. We formally tested the effect of nonlinear terms for smoking duration but found no evidence that they were associated with EAC ($p = 0.33$), GEJAC ($p = 0.32$), or ESCC ($p = 0.12$). Increasing intensity of smoking as a linear term in the model was associated with increased risk of ESCC but not EAC or GEJAC. Compared with the effects observed for smoking duration, we found weaker associations and poorer-fitting models when cumulative dose was assessed for EAC and GEJAC; for ESCC, the cumulative dose term provided a fit similar to those for duration and intensity.

When linear terms for duration and intensity were included simultaneously in the model, duration remained significantly associated with EAC (odds ratio (OR) = 1.20, 95 percent confidence interval (CI): 1.06, 1.36) and GEJAC (OR = 1.17, 95 percent CI: 1.05, 1.31) (table 3), but intensity showed no improvement in the model goodness of fit in comparison with the model that included a term only for duration (data not shown). Although the linear effect of smoking intensity showed no significant association with GEJAC, the effect became significant ($p = 0.02$) when intensity was included as a nonlinear function in the model (figure 1, part *A*) and improved the model's goodness of fit significantly ($p = 0.01$). The risk of GEJAC increased steadily by 65–70 percent for each additional increment of 10 cigarettes/day, plateaued at 25 cigarettes/day, and then declined for persons who smoked more than 30 cigarettes/day.

In contrast, when linear terms for duration and intensity were modeled simultaneously for ESCC, both retained sizeable and significant risk estimates and resulted in a better-fitting model. As for GEJAC, modeling smoking intensity as a nonlinear function significantly improved the model fit ($p = 0.05$); the odds of ESCC increased significantly by 50 percent for every extra 10 cigarettes/day, plateaued at 40 cigarettes/day, and declined slightly for persons who smoked more than 60 cigarettes/day.

Effects of smoking cessation

After partitioning of the qualitative effect of ever smoking, time since quitting was associated with significant risk reductions for all three subtypes on the order of 20 percent per 10 years of cessation, in comparison with current smokers. The risk estimate remained essentially unchanged regardless of which other dimensions of smoking were included in the models (table 3). After adjusting for intensity as a nonlinear function in the model, the effect of time since quitting was attenuated slightly for GEJAC (OR = 0.83, 95 percent CI: 0.74, 0.93) and ESCC (OR = 0.85, 95 percent CI: 0.75, 0.98), but it remained significant. The risk observed in relation to time since quitting declined in a linear fashion for all three sites ($p = 0.86$, $p = 0.18$, and $p = 0.57$ for EAC, GEJAC, and ESCC, respectively, when tested against linearity) (figure 2). Smoking intensity remained a significant risk factor for GEJAC and ESCC independently of time since quitting (table 3). Conversely, risk estimates for duration of smoking were attenuated to the null for all three cancers when the term for time since quitting was also included in the model.

DISCUSSION

We have confirmed that smoking is a sizeable and significant risk factor for each histologic subtype of esophageal cancer but have shown qualitative and quantitative differences in the associations by subtype. Thus, while duration

TABLE 3. Odds ratios for different histologic types of esophageal cancer according to various dimensions of tobacco smoking in simultaneous modeling, Australia, 2002–2005

Model*	Esophageal adenocarcinoma			Gastroesophageal junction adenocarcinoma			Esophageal squamous cell carcinoma		
	OR†,‡	95% CI†	*p* value	OR‡	95% CI	*p* value	OR‡	95% CI	*p* value
Ever smoking	1.76	1.29, 2.40	<0.001	2.38	1.78, 3.17	<0.001	2.92	2.06, 4.15	<0.001
Intensity of smoking (per 10 cigarettes/day)	0.99	0.88, 1.11	0.85	1.00	0.90, 1.12	0.96	1.17	1.04, 1.32	0.008
Duration of smoking (per 10 years)	1.20	1.06, 1.36	0.005	1.17	1.05, 1.31	0.003	1.19	1.04, 1.35	0.01
Ever smoking	1.75	1.29, 2.38	<0.001	2.33	1.74, 3.10	<0.001	2.88	2.03, 4.08	<0.001
Intensity of smoking (per 10 cigarettes/day)	1.00	0.89, 1.12	0.97	1.00	0.90, 1.12	0.96	1.18	1.05, 1.33	0.005
Time since quitting smoking (per 10 years)	0.81	0.71, 0.92	0.001	0.81	0.72, 0.90	<0.001	0.80	0.70, 0.92	0.001
Ever smoking	1.75	1.29, 2.38	<0.001	2.32	1.74, 3.09	<0.001	2.87	2.03, 4.08	<0.001
Intensity of smoking (per 10 cigarettes/day)	1.00	0.88, 1.12	0.96	1.01	0.90, 1.13	0.88	1.18	1.05, 1.33	0.005
Duration of smoking (per 10 years)	1.00	0.79, 1.27	0.97	0.94	0.77, 1.15	0.53	0.95	0.75, 1.21	0.70
Time since quitting smoking (per 10 years)	0.81	0.64, 1.03	0.08	0.76	0.62, 0.93	0.009	0.77	0.60, 0.98	0.04
Ever smoking	1.75	1.29, 2.38	<0.001	2.32	1.74, 3.09	<0.001	2.86	2.02, 4.06	<0.001
Cumulative dose (per 10 pack-years)	1.01	0.93, 1.09	0.85	0.98	0.91, 1.06	0.65	1.06	0.98, 1.15	0.16
Time since quitting smoking (per 10 years)	0.82	0.71, 0.94	0.006	0.79	0.70, 0.90	<0.001	0.82	0.71, 0.96	0.01

* All continuous smoking measures were centered (by subtracting the mean value from the original value among smokers), and estimates of odds ratios were obtained using separate models that each included an indicator variable for ever/never smoking.

† OR, odds ratio; CI, confidence interval.

‡ Adjusted for age, sex, education, frequency of aspirin use, average alcohol intake, body mass index in the past year, and frequency of heartburn or acid reflux.

and intensity of smoking were both independently associated with GEJAC and ESCC, we found no evidence that smoking intensity predicted risk of EAC. Finally, these analyses demonstrated the benefits of smoking cessation in reducing the risks of all three types of cancer, after accounting for the other qualitative and quantitative effects of smoking on cancer risk.

The role of smoking (and cessation) in the development of EAC has been of particular interest because of the substantial increase in incidence among Western populations during a period when the overall prevalence of smoking has declined. Risk estimates derived from our preliminary categorical analyses accord with previous estimates (2, 3, 8), except that in all earlier studies, investigators reported significant dose-response trends for every dimension of smoking assessed. Unlike investigators in previous studies, we found no association with age of smoking onset for any of the cancers or with smoking intensity for EAC. One likely explanation for these important differences is that earlier studies included ''never smokers'' as the reference category when testing for trend, which tends to overestimate the dose effect (11). Furthermore, to the best of our knowledge, previous investigations of smoking and esophageal cancer have not assessed the independent effect of each smoking dimension by simultaneously modeling other smoking dimensions; hence, previous dimension-specific estimates may have been confounded by other aspects of smoking exposure.

One strategy for addressing the complexity of the multidimensional nature of smoking exposure is to fit models that include both indicator terms for ever smoking and transformed variables for the continuous dimensions of smoking (11). Using this approach, our data showed that smoking duration is the key determinant of risk for adenocarcinoma, whereas intensity and duration together determine the risk of squamous cell carcinoma. These findings strongly suggest that the mechanisms by which EACs and ESCCs are induced in smokers differ. An overall stronger effect of smoking for squamous cell carcinoma as compared with adenocarcinoma has also been observed in lung cancers (4, 20, 21). However, these studies have not directly compared the effects of duration and intensity among the different histologic subtypes.

By analyzing the effects of the various dimensions of smoking using generalized additive models, we were able to explore possible nonlinear effects of these exposures on esophageal cancer risk. For most measures, we found no evidence that models incorporating nonlinear terms explained the association with esophageal cancer risk any better than linear models. However, for GEJAC and ESCC, we found that including a nonlinear term for smoking intensity produced significantly better-fitting models than those including a linear term. Nonlinear associations with smoking intensity have also been observed in lung cancer studies (4, 22) and suggest that the reduced risk of cancer among persons exposed to tobacco smoke at higher intensities may reflect increased DNA repair capacity (or reduced susceptibility to cancer) as opposed to misclassification or other sources of error.

Why should histologic subtypes of esophageal cancer have differing associations with patterns of smoking? Few directly applicable data are available; however, analogies in lung cancer epidemiology may offer insights. Similarly to esophageal cancer, there has been an increase in the ratio of adenocarcinoma to squamous cell carcinoma for lung

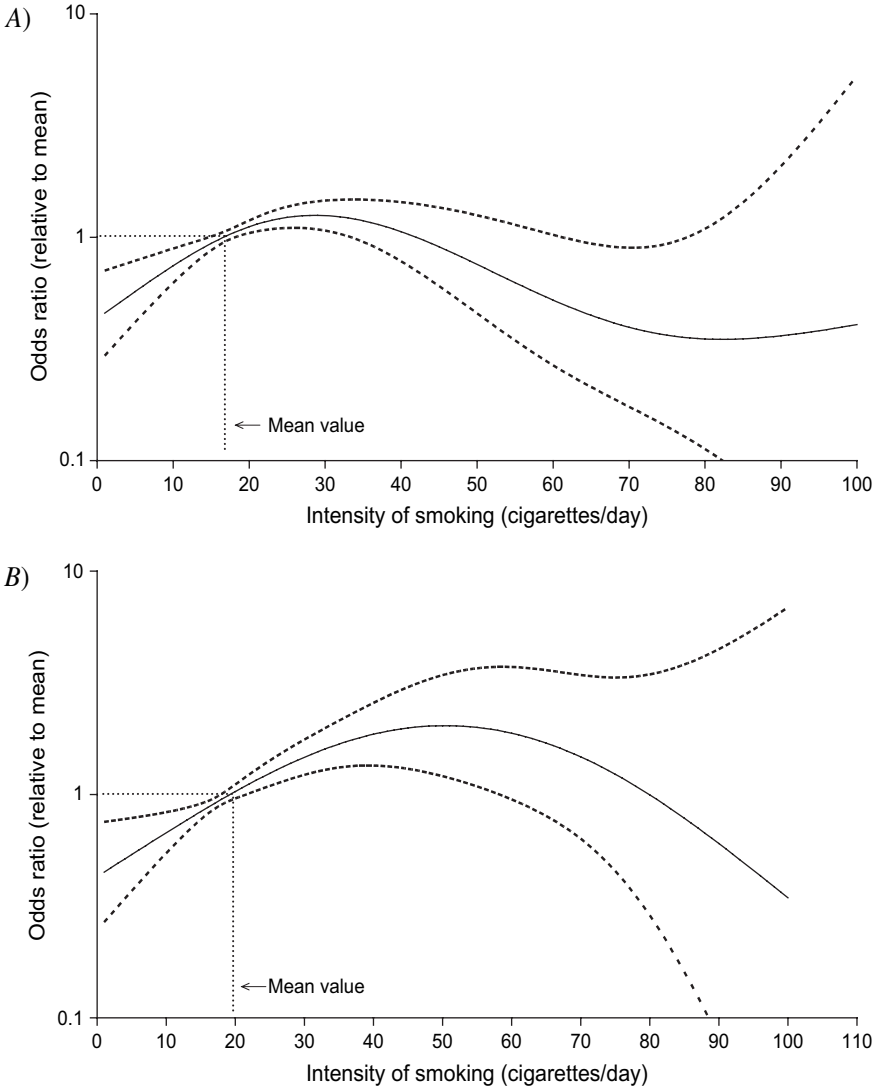


FIGURE 1. Relations of intensity of smoking and its dose-pattern effect with risks of (*A*) gastroesophageal junction adenocarcinoma and (*B*) esophageal squamous cell carcinoma, Australia, 2002–2005. Results were obtained using generalized additive logistic models with a 3-df cubic spline function. The solid line represents the odds ratio, and the dashed line represents its 95% confidence interval. The reference value for the estimate was fixed around the mean of the continuous variable; hence, the odds ratio for an association between two intensity values (*x*-axis) can be calculated as the ratio of the two corresponding odds ratios (*y*-axis, log scale).

cancer (23, 24); this has been attributed to the introduction of filter-tipped and ''low-tar'' cigarettes, which has altered the patterns of respiratory epithelial exposure to tobacco carcinogens (25, 26). Whether this pertains to esophageal cancer is not known. At the cellular level, it appears that the chromosomal aberrations caused by tobacco smoke cluster differently in adenocarcinomas and squamous cell carcinoma of the lung (27). We are not aware of comparable investigations for esophageal cancers relating to tobacco exposure, but they could be highly informative.

Host factors also play some role in determining susceptibility to the carcinogenic effects of tobacco smoke. At least one report has identified combinations of polymorphisms in DNA repair genes that are differently associated with adenocarcinomas and squamous cell carcinoma of the lung (28), suggesting that constitutional genotype may influence not only overall cancer risk but also the type and site of smoking-related cancers. Doecke et al.'s (29) recent finding that polymorphisms in the *MGMT* gene (which codes for a protein that repairs alkylating mutations arising from nitrosamines) are associated with increased risks of EAC but not GEJAC accords with this notion and provides some clues to the potential etiologic pathways of esophageal cancers.

From public health and clinical perspectives, our analyses offer hope that people who permanently cease smoking will significantly reduce their risk of all types of esophageal cancer. We estimated that the magnitude of the risk reduction was approximately 15–19 percent for every 10 years of smoking cessation. In our data set, smoking duration and time since quitting were correlated measures with effect sizes that were almost equal in opposite directions. When

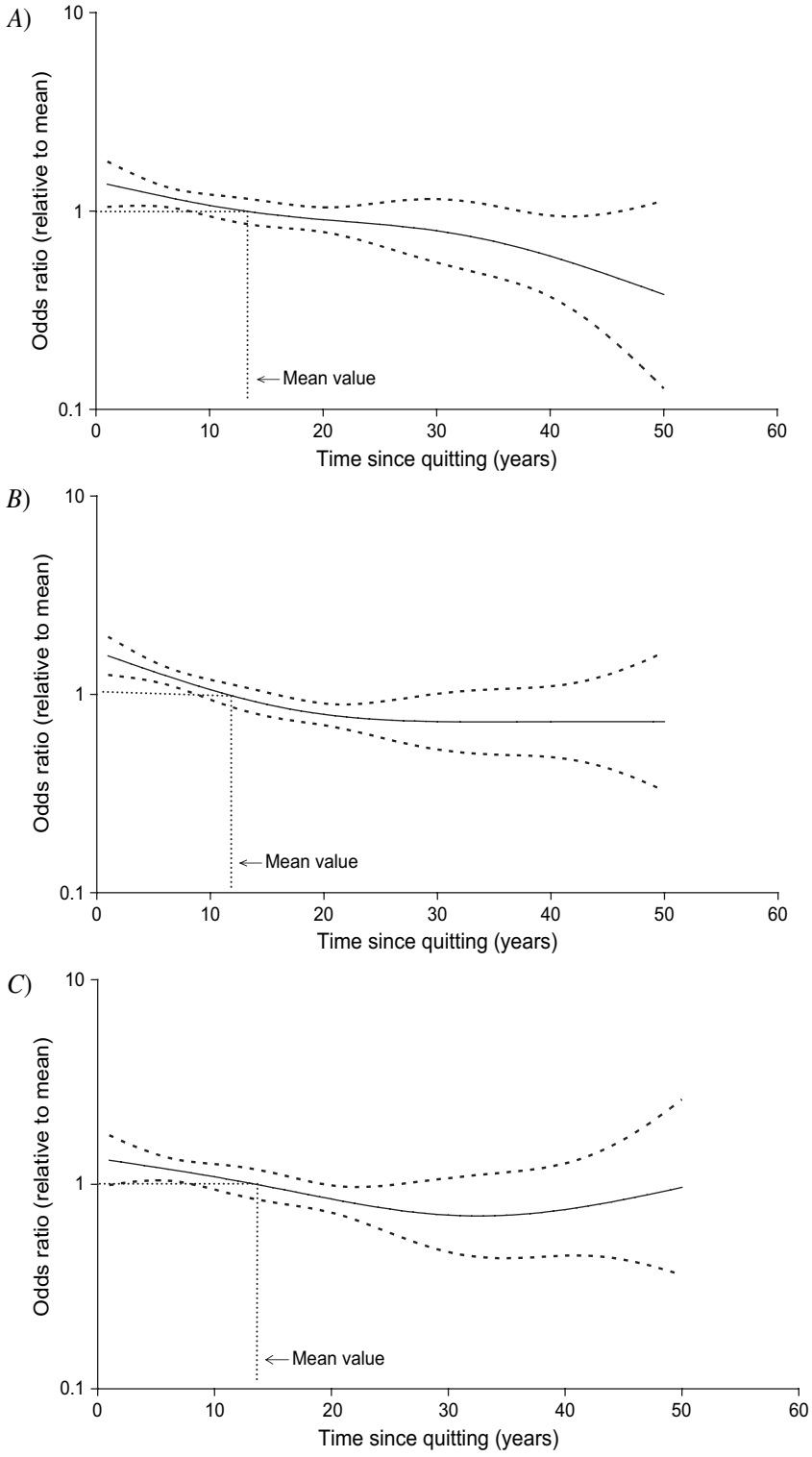


FIGURE 2. Relations of time since quitting smoking and its dose-pattern effect with risks of (*A*) esophageal adenocarcinoma, (*B*) gastroesophageal junction adenocarcinoma, and (*C*) esophageal squamous cell carcinoma, Australia, 2002–2005. Results were obtained using generalized additive logistic models with a 3-df cubic spline function. The solid line represents the odds ratio, and the dashed line represents its 95% confidence interval. The reference value for the estimate was fixed around the mean of the continuous variable; hence, the odds ratio for an association between two values for time since quitting (*x*-axis) can be calculated as the ratio of the two corresponding odds ratios (*y*-axis, log scale).

these factors were adjusted for each other, only time since quitting remained statistically significant, suggesting that this effect dominated among ex-smokers.

Strengths of our study included the large sample size, the population-based sampling frame, and the systematic collection of detailed smoking data. We minimized the

possibility of biased recall by concealing study hypotheses from participants and interviewers. Our inferences regarding the effects of smoking on esophageal cancer were strengthened by the consistent differences in associations by histologic type, a circumstance unlikely to be explained by chance or differential reporting.

A limitation of our study was the low participation rate among controls, increasing the likelihood that our control sample was not representative of the population from which the cases arose. To assess the magnitude of possible bias, we compared smoking prevalence in our control group with that reported for the 2004 Australian National Health Survey (30), a representative survey of the Australian adult population. While the distribution of overall smoking status in controls was similar to that of the overall population, ex-smokers were somewhat overrepresented among our controls. We estimated the effects of potentially biased participation by imputation analysis and found that increases in risk estimates derived from the imputed data remained over twofold and significant for both current smokers and ex-smokers. Some degree of selection bias may have also beset the cases, although its direction and magnitude are difficult to estimate. Survival bias, where cases with long survival are overrepresented in the study sample, might have been present if smoking status were associated with survival among esophageal cancer patients. We compared survival for each group of case participants according to smoking status using mortality data collected subsequently and found no significant differences within any of the case groups, suggesting that any pertinent survivor bias was unlikely to account for the different patterns of risk between the groups. We also repeated our analyses after excluding the subset of cases identified through the cancer registries (for whom longer survival might have contributed to recruitment), with little difference in estimates being observed.

In summary, we found qualitative and quantitative differences in the association between dimensions of smoking exposure and EAC, GEJAC, and ESCC. Duration of smoking was a strong determinant of all three types of cancer, but intensity was associated only with risks of GEJAC and ESCC, and there was a significant nonlinear dose effect of intensity on risk of these cancers. Time since quitting was an independent predictor for all outcomes and was the most dominant dimension of smoking. Our findings emphasize the benefits of quitting smoking in reducing the risk of esophageal cancer, irrespective of how long or how heavily a person has smoked.

ACKNOWLEDGMENTS

This study was supported by the Cancer Council Queensland and the National Health and Medical Research Council of Australia (NHMRC) (program 199600). D. C. W. and P. M. W. were supported by Senior Research Fellowships from the NHMRC and Cancer Council Queensland, respectively. N. P. was supported by a doctoral scholarship from the NHMRC. S. S. was supported by a doctoral scholarship from the Ministry of Health and Medical Education of the Islamic Republic of Iran.

The authors acknowledge Dr. Adrian Barnett (University of Queensland, Brisbane, Australia) for his help with R programming and his comments on the manuscript. Dr. Jay Lubin (National Cancer Institute, Bethesda, Maryland) provided thoughtful feedback on this work.

The funding bodies played no role in the design or conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

Conflict of interest: none declared.

REFERENCES

1. Vaughan TL, Davis S, Kristal A, et al. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. Cancer Epidemiol Biomarkers Prev 1995;4:85–92.
2. Gammon MD, Schoenberg JB, Ahsan H, et al. Tobacco, alcohol, and socioeconomic status and adenocarcinomas of the esophagus and gastric cardia. J Natl Cancer Inst 1997;89:1277–84.
3. Lagergren J, Bergstrom R, Lindgren A, et al. The role of tobacco, snuff and alcohol use in the aetiology of cancer of the oesophagus and gastric cardia. Int J Cancer 2000;85:340–6.
4. Lubin JH, Caporaso NE. Cigarette smoking and lung cancer: modeling total exposure and intensity. Cancer Epidemiol Biomarkers Prev 2006;15:517–23.
5. Hashibe M, Boffetta P, Janout V, et al. Esophageal cancer in Central and Eastern Europe: tobacco and alcohol. Int J Cancer 2007;120:1518–22.
6. Lindblad M, Rodriguez LAG, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. Cancer Causes Control 2005;16:285–94.
7. Cheng KK, Sharp L, McKinney PA, et al. A case-control study of oesophageal adenocarcinoma in women: a preventable disease. Br J Cancer 2000;83:127–32.
8. Wu AH, Wan P, Bernstein L. A multiethnic population-based study of smoking, alcohol and body size and risk of adenocarcinomas of the stomach and esophagus (United States). Cancer Causes Control 2001;12:721–32.
9. Freedman ND, Abnet CC, Leitzmann MF, et al. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. Am J Epidemiol 2007;165:1424–33.
10. Anderson LA, Watson RG, Murphy SJ, et al. Risk factors for Barrett's oesophagus and oesophageal adenocarcinoma: results from the FINBAR study. World J Gastroenterol 2007;13:1585–94.
11. Leffondré K, Abrahamowicz M, Siemiatycki J, et al. Modeling smoking history: a comparison of different approaches. Am J Epidemiol 2002;156:813–23.
12. Leffondré K, Abrahamowicz M, Xiao Y, et al. Modelling smoking history using a comprehensive smoking index: application to lung cancer. Stat Med 2006;25:4132–46.
13. Whiteman DC, Sadeghi S, Pandeya N, et al. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. Gut 2008;57:173–80.
14. Olsen CM, Bain CJ, Jordan SJ, et al. Recreational physical activity and epithelial ovarian cancer: a case-control study, systematic review, and meta-analysis. Cancer Epidemiol Biomarkers Prev 2007;16:2321–30.
15. Rachet B, Siemiatycki J, Abrahamowicz M, et al. A flexible modeling approach to estimating the component effects of

smoking behavior on lung cancer. J Clin Epidemiol 2004;57:1076–85.
16. Kraemer HC, Blasey CM. Centering in regression analyses: a strategy to prevent errors in statistical inference. Int J Methods Psychiatr Res 2004;13:141–51.
17. Hastie TJ, Tibshirani RJ. Generalized additive models. (Monographs on statistics and applied probability, no. 43). London, United Kingdom: Chapman & Hall Ltd, 1990.
18. R Development Core Team. R: a language and environment for statistical computing (version 2.3.1). (ISBN 3-900051-07-0). Vienna, Austria: R Foundation for Statistical Computing, 2006. (http://www.R-project.org).
19. Wood SN. Generalized additive models: an introduction with R. (Texts in statistical science). Boca Raton, FL: CRC Press, 2006.
20. Khuder SA. Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. Lung Cancer 2001;31:139–48.
21. Jedrychowski W, Becher H, Wahrendorf J, et al. Effect of tobacco smoking on various histological types of lung cancer. J Cancer Res Clin Oncol 1992;118:276–82.
22. Lubin JH, Caporaso N, Wichmann HE, et al. Cigarette smoking and lung cancer: modeling effect modification of total exposure and intensity. Epidemiology 2007;18:639–48.
23. Li X, Mutanen P, Hemminki K. Gender-specific incidence trends in lung cancer by histological type in Sweden, 1958–1996. Eur J Cancer Prev 2001;10:227–35.
24. Blizzard L, Dwyer T. Lung cancer incidence in Australia: impact of filter-tip cigarettes with unchanged tar yields. Int J Cancer 2002;97:679–84.
25. Djordjevic MV, Hoffmann D, Hoffmann I. Nicotine regulates smoking patterns. Prev Med 1997;26:435–40.
26. De Stefani E, Boffetta P, Ronco AL, et al. Squamous and small cell carcinomas of the lung: similarities and differences concerning the role of tobacco smoking. Lung Cancer 2005;47:1–8.
27. Pan H, Califano J, Ponte JF, et al. Loss of heterozygosity patterns provide fingerprints for genetic heterogeneity in multistep cancer progression of tobacco smoke-induced non-small cell lung cancer. Cancer Res 2005;65:1664–9.
28. Popanda O, Schattenberg T, Phong CT, et al. Specific combinations of DNA repair gene variants and increased risk for non-small cell lung cancer. Carcinogenesis 2004;25:2433–41.
29. Doecke J, Zhao ZZ, Pandeya N, et al. Polymorphisms in *MGMT* and DNA repair genes and the risk of esophageal adenocarcinoma. Int J Cancer 2008;Apr 3 [Epub ahead of print].
30. Australian Bureau of Statistics. National Health Survey: users' guide—electronic publication, 2004–05. (Catalogue no. 4363.0.55.001). Canberra, Australia: Australian Bureau of Statistics, 2006. (http://www.abs.gov.au/ausstats/abs@.nsf/mf/4363.0.55.001).

Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus

D C Whiteman,[1] S Sadeghi,[1,2] N Pandeya,[1,2] B M Smithers,[3] D C Gotley,[3] C J Bain,[2] P M Webb,[1] A C Green,[1] for the Australian Cancer Study

[1] Queensland Institute of Medical Research, Brisbane, Australia; [2] School of Population Health, University of Queensland, Brisbane, Australia; [3] School of Medicine, University of Queensland, Brisbane, Australia

Correspondence to: Dr D C Whiteman, Division of Population Studies and Human Genetics, Queensland Institute of Medical Research, PO Royal Brisbane Hospital, Queensland 4029, Australia; david.whiteman@qimr.edu.au

The Australian Cancer Study: Oesophageal Cancer

Investigators : David C Whiteman MBBS, PhD; Penelope M Webb MA, D Phil; Adele C Green MBBS, PhD; Nicholas K Hayward PhD; Peter G Parsons PhD; David M Purdie PhD

Clinical collaborators: B Mark Smithers FRACS; David Gotley FRACS, PhD; Andrew Clouston FRCAP, PhD; Ian Brown FRCAP

Project manager: Suzanne Moore RN, MPH

Database: Karen Harrap BIT; Troy Sadkowski BIT

Research nurses: Suzanne O'Brien RN, MPH; Ellen Minehan RN; Deborah Roffe RN; Sue O'Keefe RN; Suzanne Lipshut RN; Gabby Connor RN; Hayley Berry RN; Frances Walker RN; Teresa Barnes RN; Janine Thomas RN; Linda Terry RN, MPH; Michael Connard BSc; Leanne Bowes BSc; MaryRose Malt RN; Jo White RN

Revised 22 July 2007
Accepted 7 August 2007
Published Online First 11 October 2007

ABSTRACT

Objective: To measure the relative risks of adenocarcinomas of the oesophagus and gastro-oesophageal junction associated with measures of obesity, and their interactions with age, sex, gastro-oesophageal reflux symptoms and smoking.

Design and setting: Population-based case–control study in Australia.

Patients: Patients with adenocarcinomas of the oesophagus (n = 367) or gastro-oesophageal junction (n = 426) were compared with control participants (n = 1580) sampled from a population register.

Main outcome measure: Relative risk of adenocarcinoma of the oesophagus or gastro-oesophageal junction.

Results: Risks of oesophageal adenocarcinoma increased monotonically with body mass index (BMI) (p_{trend} <0.001). Highest risks were seen for BMI ⩾40 kg/m^2 (odds ratio (OR) = 6.1, 95% CI 2.7 to 13.6) compared with "healthy" BMI (18.5–24.9 kg/m^2). Adjustment for gastro-oesophageal reflux and other factors modestly attenuated risks. Risks associated with obesity were substantially higher among men (OR = 2.6, 95% CI 1.8 to 3.9) than women (OR = 1.4, 95% CI 0.5 to 3.5), and among those aged <50 years (OR = 7.5, 95% CI 1.7 to 33.0) than those aged ⩾50 years (OR = 2.2, 95% CI 1.5 to 3.1). Obese people with frequent symptoms of gastro-oesophageal reflux had significantly higher risks (OR = 16.5, 95% CI 8.9 to 30.6) than people with obesity but no reflux (OR = 2.2, 95% CI 1.1 to 4.3) or reflux but no obesity (OR = 5.6, 95% 2.8 to 11.3), consistent with a synergistic interaction between these factors. Similar associations, but of smaller magnitude, were seen for gastro-oesophageal junction adenocarcinomas.

Conclusions: Obesity increases the risk of oesophageal adenocarcinoma independently of other factors, particularly among men. From a clinical perspective, these data suggest that patients with obesity and frequent symptoms of gastro-oesophageal reflux are at especially increased risk of adenocarcinoma.

The incidence of adenocarcinomas of the oesophagus and the gastro-oesophageal junction has been rising in many countries,[1–4] in some populations faster than for any other major cancer.[5] In contrast, the incidence of oesophageal squamous cell carcinoma (SCC) has remained stable or even declined in the same populations over the same periods. Such widespread changes in occurrence imply a profound shift in the prevalence of causal exposures, given no equivalent systematic changes in detection or diagnosis.[5]

Epidemiological studies strongly implicate gastro-oesophageal reflux as the primary causal factor for oesophageal adenocarcinoma[6 7] and, to a lesser extent, adenocarcinomas of the gastro-oesophageal junction. Obesity and overweight are associated with an increased prevalence of gastro-oesophageal reflux symptoms,[8–14] and thus gastro-oesophageal reflux has been widely (although not universally[15]) assumed to explain the observed increase in risk of oesophageal adenocarcinoma associated with higher levels of body mass.[16–20] However, obesity has been linked with markedly increased risks of other cancers,[21 22] and thus there are plausible grounds for speculating that high levels of body fat may promote carcinogenesis through other pathways.[23] These alternative causal hypotheses remain largely untested for oesophageal cancers.

Here, we report the findings of a large population-based case–control study evaluating the effects of obesity on the risk of adenocarcinomas of the oesophagus and gastro-oesophageal junction, alone and in combination with other causal factors.

PATIENTS AND METHODS

Approval to undertake the study was obtained from the research ethics committees of the Queensland Institute of Medical Research and participating hospitals. We obtained written informed consent from case patients and control participants to take part.

Study participants

Patients eligible for inclusion were those people aged 18–79 years with a histologically confirmed primary invasive adenocarcinoma or squamous cell carcinoma of the oesophagus or gastro-oesophageal junction diagnosed from 1 July 2001 (in Queensland) or 1 July 2002 (in the other mainland states of Australia) until 30 June 2005. The principal mode of ascertainment was via major treatment centres throughout Australia; those missed at these centres were identified by state-based cancer registries (notification of cancer diagnosis is mandatory in all states of Australia).

We identified 1610 eligible patients with a primary diagnosis of oesophageal cancer attending treatment centres during the study period. Of these, doctors refused contact with 71 patients and 167 died before consent could be obtained. A further 181 patients were excluded because they were too ill (91), mentally incapable (23), could not read or write in English (41) or were uncontactable (26). The remaining 1191 patients were invited to participate, and of these, 928 (78% of those invited) agreed to take part.

Table 1 Characteristics of study participants

		Controls		Adenocarcinoma of the oesophagus		Adenocarcinoma of the gastro-oesophageal junction	
		Men	Women	Men	Women	Men	Women
		(n = 1040)	(n = 540)	(n = 330)	(n = 37)	(n = 370)	(n = 56)
Age	Mean (SD)	62.5 (10.5)	56.7 (12.8)	63.5 (9.3)	65.6 (11.9)	63.6 (9.6)	61.8 (10.5)
Educational level (%)	School	35.9	50.6	43.6	64.9	37.3	58.9
	Trade	29.1	10.0	29.1	18.9	28.4	14.3
	Diploma	18.4	25.9	20.0	13.5	22.7	19.6
	Degree	16.4	13.3	6.7	2.7	11.1	7.1
	Not stated	0.3	0.2	0.6	0	0.5	0
BMI last year	Mean (SD)	26.9 (4.2)	26.9 (5.7)	29.1 (5.0)	29.6 (8.3)	28.3 (4.7)	28.8 (6.1)
Maximum BMI	Mean (SD)	28.5 (4.6)	28.7 (6.1)	30.8 (5.0)	32.1 (8.5)	29.8 (4.7)	31.3 (7.1)
BMI age 20 years	Mean (SD)	23.0 (3.3)	21.6 (3.4)	23.9 (3.6)	22.5 (3.5)	23.6 (3.1)	23.0 (3.7)
Smoking status	Never smoker	37.2	59.8	23.9	40.5	20.8	35.7
	Quit >20 years	28.1	13.7	25.2	16.2	28.4	14.3
	Quit 1–20 years	19.8	12.6	31.2	16.2	23.5	17.9
	Current	13.1	13.3	19.1	27.0	26.5	32.1
Cumulative smoking history (pack-years)	Never smoker	37.2	59.8	23.9	40.5	20.8	35.7
	1–14	25.2	24.6	20.0	18.9	20.0	21.4
	15–29	15.0	9.4	19.1	16.2	22.7	17.9
	30–49	13.2	3.7	22.4	16.2	22.4	23.2
	50+	9.4	2.4	14.6	8.1	14.0	1.8
Frequency of reflux symptoms 10 years ago	Never	42.1	48.2	21.5	29.7	27.0	35.7
	<Weekly	45.1	40.2	36.4	21.6	35.7	32.1
	≥Weekly	11.9	11.3	41.5	43.2	36.8	30.4
Mean alcohol consumption (10 g alcohol units/week)	Never drinker	9.5	25.7	7.3	24.3	6.8	25.0
	<1 Drink/week	1.5	5.7	2.4	0	0.8	5.4
	1–6 Drinks/week	24.6	44.4	19.4	56.8	25.7	44.6
	7–20 Drinks/week	36.8	21.5	37.3	18.9	36.2	23.2
	21+ Drinks/week	27.5	2.6	33.3	0	30.5	1.8
Frequency of aspirin use	Never	39.2	53.0	45.2	62.1	45.1	44.6
	Occasional	40.5	34.6	33.6	27.0	34.3	33.9
	<Weekly	4.5	2.8	6.1	2.7	3.8	7.1
	≥Weekly	15.6	9.3	14.2	8.1	15.7	14.3

Column percentages may not sum to 100% owing to rounding and missing values.

A further 739 alive and eligible patients were identified by the cancer registries (835 potentially eligible patients died before being identified by the cancer registries), and of these, treating doctors refused contact for 84 patients, 37 patients were incapable of taking part and 232 patients were unable to be contacted. The remaining 386 cancer registry patients were invited to take part, of whom 253 agreed (66% of those invited). Thus, a total of 1181 patients with oesophageal cancer consented to take part in the study (928 clinic patients and 253 registry patients). Questionnaires were returned by 1102 patients (367 and 426 with adenocarcinomas of the oesophagus and gastro-oesophageal junction respectively, and 309 patients with SCC).

Potential controls were randomly selected from the Australian Electoral Roll (enrolment is compulsory). We prospectively sampled controls from within strata of age (in 5-year age groups) and state of residence to match the distribution of the case series. We aimed for similar numbers of male cases and controls in each stratum of age and state; female controls were intentionally oversampled at all ages to accommodate their simultaneous enrolment in a parallel case–control study of ovarian cancer.[24]

Of 3258 potentially eligible control participants, 41 could not be contacted and 175 were excluded because they had died (16), were too ill (61), or unable to read or write in English (98). Of 3042 controls meeting the inclusion criteria, 1680 (55%) gave their consent to take part. Completed questionnaires were returned by 1580 controls (48% of all potentially eligible controls selected from the roll).

Data collection

Data were collected from all participants through self-completed, mailed questionnaires. This was followed by a telephone interview to record detailed information about past use of drugs, as well as to clarify issues arising from the self-completed questionnaires, as needed. The questionnaire elicited information about social background (education, occupation, income), as well as height and weight 1 year ago (1 year before diagnosis for cases), maximum ever weight and weight at age 20 years. We calculated the body mass index (BMI) by dividing weight in kilograms by the square of height in metres. Standard BMI categories were used for analysis (<18.5 kg/m^2, "underweight"; 18.5–24.9 kg/m^2, "healthy weight"; 25–29.9 kg/m^2, "overweight"; 30–34.9 kg/m^2, "obese I", 35–39.9 kg/m^2 "obese II" and ≥40 kg/m^2 "obese III").

Participants were asked whether, over their whole life, they had ever smoked more than 100 cigarettes, cigars, or pipes; positive responses elicited further questions about ages starting and stopping smoking and typical daily consumption. We derived the number of pack-years of tobacco exposure by dividing the number of cigarettes smoked daily by 20 and

Table 2 Relative risk for adenocarcinomas of the oesophagus and gastro-oesophageal junction associated with measures of body mass index (BMI) at different time points

	Oesophageal adenocarcinoma			Gastro-oesophageal junction adenocarcinoma		
		Fully adjusted, except reflux*	Fully adjusted, with reflux†		Fully adjusted, except reflux†	Fully adjusted, with reflux
	Controls/Cases	OR (95% CI)	OR (95% CI)	Cases	OR (95% CI)	OR (95% CI)
BMI last year (kg/m^2)						
<18.5	21/1	0.3 (0.0 to 2.6)	0.5 (0.1 to 3.6)	1	0.2 (0.0 to 1.7)	0.3 (0.0 to 2.0)
18.5–24.9	528/71	1.0 (ref)	1.0 (ref)	107	1.0 (ref)	1.0 (ref)
25.0–29.9	650/150	1.4 (1.0 to 1.9)	1.2 (0.9 to 1.7)	168	1.1 (0.8 to 1.4)	1.0 (0.7 to 1.3)
30.0–34.9	222/89	2.7 (1.8 to 3.9)	2.1 (1.4 to 3.1)	98	1.9 (1.3 to 2.6)	1.6 (1.1 to 2.2)
35.0–39.9	68/25	3.1 (1.8 to 5.5)	2.5 (1.4 to 4.4)	27	2.0 (1.2 to 3.4)	1.7 (1.0 to 3.0)
40+	24/16	7.0 (3.3 to 15.0)	6.1 (2.7 to 13.6)	9	2.6 (1.1 to 6.2)	2.4 (1.0 to 5.8)
p trend		<0.001	<0.001		<0.001	<0.001
BMI maximum (kg/m^2)						
<18.5	9/1	0.9 (0.1 to 8.7)	1.4 (0.2 to 11.9)	0	–	–
18.5–24.9	356/39	1.0 (ref)	1.0 (ref)	55	1.0 (ref)	1.0 (ref)
25.0–29.9	708/136	1.4 (0.9 to 2.0)	1.2 (0.8 to 1.7)	178	1.3 (0.9 to 1.8)	1.1 (0.8 to 1.6)
30.0–34.9	333/114	2.5 (1.6 to 3.7)	1.9 (1.3 to 3.0)	122	1.9 (1.3 to 2.7)	1.6 (1.1 to 2.4)
35.0–39.9	107/43	4.1 (2.4 to 6.8)	3.1 (1.8 to 5.3)	47	2.9 (1.8 to 4.6)	2.4 (1.5 to 3.9)
40+	52/24	5.2 (2.7 to 9.9)	4.4 (2.3 to 8.7)	15	2.1 (1.1 to 4.2)	1.9 (1.0 to 3.8)
p trend		<0.001	<0.001		<0.001	<0.001
BMI age 20 years (kg/m^2)						
<18.5	121/14	0.8 (0.4 to 1.4)	0.8 (0.5 to 1.6)	9	0.4 (0.2 to 0.8)	0.4 (0.2 to 0.8)
18.5–24.9	1144/227	1.0 (ref)	1.0 (ref)	282	1.0 (ref)	1.0 (ref)
25.0–29.9	237/81	1.7 (1.2 to 2.3)	1.7 (1.2 to 2.3)	97	1.6 (1.2 to 2.1)	1.6 (1.2 to 2.2)
30.0–34.9	29/13	2.6 (1.3 to 5.2)	2.4 (1.1 to 5.1)	13	2.1 (1.0 to 4.1)	2.0 (0.9 to 4.1)
35.0+	6/5	3.6 (1.0 to 13.0)	2.9 (0.8 to 11.2)	2	1.1 (0.2 to 5.9)	1.0 (0.2 to 5.3)
p trend		<0.001	<0.001		<0.001	<0.001
Change in BMI (kg/m^2)						
<3	581/98	1.0 (ref)	1.0 (ref)	131	1.0 (ref)	1.0 (ref)
3–4.9	338/73	1.2 (0.9 to 1.7)	1.0 (0.7 to 1.5)	96	1.1 (0.8 to 1.6)	1.0 (0.7 to 1.4)
5–9.9	406/117	1.7 (1.3 to 2.4)	1.4 (1.0 to 2.0)	115	1.2 (0.9 to 1.6)	1.1 (0.8 to 1.5)
10+	153/47	2.2 (1.4 to 3.4)	1.8 (1.2 to 2.8)	50	1.6 (1.0 to 2.3)	1.4 (0.9 to 2.1)
p trend		<0.001	0.002		0.05	0.26

*Adjusted for age, sex, state, household income, cumulative smoking history, mean alcohol consumption and frequency of aspirin use in the 5 years before diagnosis.
†Adjusted for above factors and frequency of gastro-oesophageal reflux symptoms 10 years before diagnosis.

multiplying by the total number of years smoked. For analysis, "never smokers" were the reference category and "ever smokers" were categorised according to total pack-years of smoking.

We asked participants to report the frequency with which they consumed different classes of alcohol (low-alcohol beer, regular beer, white wine, red wine, port/sherry and spirits/liqueurs) between ages 20–29, 30–49 and ⩾50 years, as applicable. Total alcohol consumption was summed across all age groups for all types of alcohol, from which we calculated a weighted average number of standard drinks (10 g ethanol) consumed each week between age 20 years and current age.

We assessed the frequency of symptoms of gastro-oesophageal reflux 10 years before diagnosis, defined as the presence of heartburn ("a burning pain behind the breastbone after eating") or acid reflux ("a sour taste from acid or bile rising up into the mouth or throat"). For analysis, we used the highest reported frequency for either symptom and defined "frequent symptoms" as those occurring at least weekly.[9 10] Frequency of aspirin intake during the past 5 years was ascertained on a scale ranging from "never" to "two or more times/day".

Details of the histological type and anatomical site of each tumour were abstracted from diagnostic pathology reports. Anatomical sites of tumours were categorised according to the WHO classification[25] into "oesophageal" and "gastro-oesophageal junction" tumours.

Statistical analyses

We calculated the odds ratio (OR) and 95% confidence interval (95% CI) associated with each exposure using multivariable logistic regression analysis in SAS version 9.1 (SAS Institute, Inc, Cary NC, USA). Statistical significance was determined at $\alpha = 0.05$, and all tests for statistical significance were two sided. Our approach was first, to fit minimally adjusted models which contained terms for each exposure and the matching variables (sex, age and state). We then estimated relative risks associated with BMI adjusted for these variables and income, smoking, alcohol consumption and frequency of aspirin use. Finally, we fitted fully adjusted models which included the preceding variables as well as a term for frequency of gastro-oesophageal reflux symptoms. For each variable, the lowest category was the reference category, except for BMI for which the reference was the healthy weight range. We tested for trend by including each category as an ordinal variable in the multivariable model, with category values taken as the midpoint of the range. For variables in which the lowest category was "unexposed" (eg, pack-years of smoking), trend tests were restricted to the "exposed" categories.

To assess potential interactions between BMI and reflux or smoking, we created new variables that reclassified participants according to their combined exposure to BMI and the other factors. Risks for each category of combined exposure were estimated relative to the reference category in multivariable

Table 3 Relative risks for adenocarcinomas of the oesophagus and gastro-oesophageal junction associated with body mass index in the year before diagnosis, stratified by sex and age

		Oesophageal adenocarcinoma		Gastro-oesophageal junction adenocarcinoma		
		Fully adjusted, except reflux*	Fully adjusted, with reflux†		Fully adjusted, except reflux	Fully adjusted, with reflux
BMI	Controls/cases	OR (95% CI)	OR (95% CI)	Cases	OR (95% CI)	OR (95% CI)
Women						
<25.0	224/12	1.0 (ref)	1.0 (ref)	16	1.0 (ref)	1.0 (ref)
25.0–29.9	166/8	0.5 (0.2 to 1.5)	0.5 (0.2 to 1.5)	18	1.0 (0.6 to 2.7)	1.2 (0.5 to 2.5)
≥30.0	125/13	1.7 (0.7 to 4.1)	1.4 (0.5 to 3.5)	22	2.3 (1.1 to 4.7)	1.9 (0.9 to 4.1)
Men						
<25.0	325/60	1.0 (ref)	1.0 (ref)	92	1.0 (ref)	1.0 (ref)
25.0–29.9	484/142	1.6 (1.1 to 2.2)	1.3 (0.9 to 1.9)	150	1.1 (0.8 to 1.5)	1.0 (0.7 to 1.4)
≥30.0	189/117	3.3 (2.3 to 4.8)	2.6 (1.8 to 3.9)	112	2.1 (1.5 to 2.9)	1.7 (1.2 to 2.5)
Age <50 years						
<25.0	127/5	1.0 (ref)	1.0 (ref)	9	1.0 (ref)	1.0 (ref)
25.0–29.9	94/10	1.8 (0.5 to 6.7)	1.4 (0.3 to 5.5)	20	1.8 (0.7 to 4.7)	1.3 (0.5 to 3.8)
≥30.0	49/14	10.5 (2.7 to 40.9)	7.5 (1.7 to 33.0)	14	3.9 (1.3 to 11.6)	3.5 (1.1 to 11.4)
Age ≥50 years						
<25.0	422/67	1.0 (ref)	1.0 (ref)	99	1.0 (ref)	1.0 (ref)
25.0–29.9	556/140	1.4 (1.0 to 2.0)	1.2 (0.9 to 1.7)	148	1.1 (0.8 to 1.5)	1.0 (0.7 to 1.3)
≥30.0	265/116	2.8 (1.9 to 3.9)	2.2 (1.5 to 3.1)	120	1.9 (1.4 to 2.7)	1.6 (1.2 to 2.3)

*Adjusted for age (in years), sex, state of residence, household income, cumulative smoking history, mean alcohol consumption and frequency of aspirin use in the 5 years before diagnosis.
†Adjusted for above factors and frequency of gastro-oesophageal reflux symptoms 10 years before diagnosis.

logistic regression analyses. To quantify biological interaction, we calculated the synergy index *S*[26] using the algorithm of Andersson.[27]

RESULTS

Table 1 presents the distribution of salient characteristics of cases and controls. Female controls were younger on average than female case patients owing to their simultaneous sampling for a related study of ovarian cancer.

BMI and risk of adenocarcinoma of the oesophagus

In multivariable models adjusting for age, sex, income, smoking, alcohol and aspirin consumption, we found that people who were overweight had modestly increased risks of oesophageal adenocarcinoma compared with the reference category, and risks increased with increasing BMI (p_{trend} <0.001). Severely obese people (BMI ≥40 kg/m^2) had a sevenfold increased risk of adenocarcinoma compared with people in the healthy weight range. Further adjustment for symptoms of reflux attenuated the association only modestly, and relative risks for the severely obese category remained very high (table 2). Collapsing the three obese categories into a single group (ie, BMI ≥30 kg/m^2) yielded a crude risk estimate of 3.3 (95% CI 2.3 to 4.6) which reduced to 2.4 (95% CI 1.7 to 3.5) after full adjustment.

Patterns of risk associated with maximum ever BMI were similar to those seen for BMI in the year before diagnosis. Fully adjusting for confounding factors reduced the risk estimates somewhat; however, significant, dose-dependent associations with BMI persisted (p_{trend} <0.001). At age 20 years, the distribution of BMI was narrow with fewer than 20% of controls reportedly overweight or obese. Nevertheless, we observed significant trends of increasing risk with successively higher BMI categories at this age group, even after fully adjusting for other factors (table 2).

Weight gain during adulthood was associated with modestly increased risks of oesophageal adenocarcinoma, although this was statistically significant only for marked increases in BMI (>5 kg/m^2) after adjusting for confounding factors (table 2). As the magnitude of the effect for BMI in the year before diagnosis was largest and remained highly significant after adjusting for the other BMI terms, we used this measure for subsequent analyses.

BMI and risk of adenocarcinoma of the gastro-oesophageal junction

Significant trends of increasing risk of adenocarcinoma of the gastro-oesophageal junction with increasing BMI were seen, although the overall magnitude of risks was substantially lower than for oesophageal adenocarcinomas (table 2), and this approached statistical significance for measures of BMI in the year before diagnosis (p = 0.080) and maximum ever BMI (p = 0.075). Again, adjusting for gastro-oesophageal reflux and other factors led to modest attenuation of effects. Large increases in weight gain since age 20 years were associated with non-significantly increased risks of gastro-oesophageal adenocarcinoma.

Effects of sex and age

In stratified analyses, the risks of oesophageal adenocarcinoma associated with BMI were higher among men than women, and were higher among those aged <50 years than those aged ≥50 years (table 3). Similar patterns of effect modification were seen for gastro-oesophageal junction adenocarcinomas.

Combined effects of obesity and gastro-oesophageal reflux

Risks of oesophageal adenocarcinoma increased with increasing frequency of reflux symptoms (“Overall association”, table 4). After reclassifying participants according to their BMI category (“healthy”, “overweight” or “obese”) combined with their reflux symptoms frequency (“none”, “less than weekly”, “at least weekly”), we observed stepwise increases in the risk of oesophageal adenocarcinoma with increasing BMI among those with no reflux symptoms (table 4). Similarly, risks of oesophageal adenocarcinoma increased steadily with reflux

Table 4 Relative risks for adenocarcinomas of the oesophagus and gastro-oesophageal junction associated with symptoms of gastro-oesophageal reflux or smoking, overall and combined with body mass index (BMI) category

			Reflux combined with BMI					
	Reflux overall association		BMI <25		BMI 25–24.9		BMI ≥30	
Frequency of reflux	Controls/cases	OR* (95% CI)	Controls/cases	OR† (95% CI)	Controls/cases	OR (95% CI)	Controls/cases	OR (95% CI)
Adenocarcinoma oesophagus								
Never	698/82	1.0 (ref)	279/22	1.0 (ref)	253/36	1.6 (0.9 to 2.8)	122/20	2.2 (1.1 to 4.3)
<Weekly	686128	1.5 (1.1 to 2.0)	218/26	1.4 (0.8 to 2.7)	320/53	1.8 (1.1 to 3.2)	143/46	3.9 (2.2 to 7.0)
≥Weekly	184/153	6.4 (4.5 to 9.0)	52/24	5.6 (2.8 to 11.3)	77/59	7.4 (4.1 to 13.5)	49/64	16.5 (8.9 to 30.6)
Adenocarcinoma gastro-oesophageal junction								
Never	698/120	1.0 (ref)	279/38	1.0 (ref)	253/36	0.8 (0.5 to 1.4)	122/40	2.1 (1.3 to 3.6)
<Weekly	686/150	1.1 (0.9 to 1.5)	218/40	1.2 (0.7 to 1.9)	320/58	1.0 (0.7 to 1.7)	143/47	1.9 (1.2 to 3.2)
≥Weekly	184/153	4.5 (3.3 to 6.1)	52/28	3.6 (2.0 to 6.7)	77/74	5.5 (3.3 to 8.9)	49/47	5.8 (3.3 to 10.1)
			Smoking combined with BMI					
	Smoking overall association		**BMI <25**		**BMI 25–24.9**		**BMI ≥30**	
Smoking history	**Controls/cases**	**OR (95% CI)**	**Controls/cases**	**OR‡ 95% CI†)**	**Controls/cases**	**OR (95% CI)**	**Controls/cases**	**OR (95% CI)**
Adenocarcinoma oesophagus								
Never smoker	710/94	1.0 (ref)	277/22	1.0 (ref)	274/35	1.2 (0.7 to 2.3)	127/34	3.5 (1.9 to 6.6)
1–29 Pack-years	602/142	1.4 (1.0 to 2.0)	185/19	1.2 (0.6 to 2.4)	272/63	2.0 (1.1 to 3.5)	117/56	3.8 (2.1 to 6.9)
30+ Pack-years	268/131	2.3 (1.6 to 3.3)	87/31	3.0 (1.5 to 5.8)	104/52	3.5 (1.9 to 6.5)	70/40	3.8 (2.0 to 7.4)
Adenocarcinoma gastro-oesophageal junction								
Never smoker	710/97	1.0 (ref)	277/34	1.0 (ref)	274/33	0.9 (0.5 to 1.6)	127/25	1.9 (1.1 to 3.5)
1–29 Pack-years	602/180	2.1 (1.5 to 2.8)	185/35	1.8 (1.0 to 3.1)	272/82	2.0 (1.2 to 3.2)	117/58	3.6 (2.2 to 6.1)
30+ Pack-years	268/149	3.2 (2.3 to 4.6)	87/39	3.2 (1.8 to 5.8)	104/53	3.1 (1.8 to 5.4)	70/51	4.6 (2.6 to 8.1)

*Odds ratio and 95% confidence interval adjusted for age (in years), sex, income, state of residence, cumulative smoking history, alcohol consumption, frequency of aspirin use in the past 5 years, frequency of gastro-oesophageal reflux symptoms 10 years before diagnosis and BMI in the year before diagnosis.
†Odds ratio and 95% confidence interval adjusted for age (in years), sex, income, state of residence, cumulative smoking history, alcohol consumption and frequency of aspirin use in the past 5 years.
‡Odds ratio adjusted for age (in years), sex, income, state of residence, frequency of gastro-oesophageal reflux symptoms 10 years before diagnosis, alcohol consumption and frequency of aspirin use in the past 5 years.

frequency among those in the "healthy" BMI range. People in the highest combined exposure category (ie, BMI ≥30.0 with at least weekly symptoms of reflux) had significantly higher risks of oesophageal adenocarcinoma than people with only one of these conditions. Risks of combined exposure were almost threefold higher than expected assuming additive interactions ($S = 2.7$, 95% CI 1.3 to 5.4).

Risks of gastro-oesophageal junction adenocarcinomas were also substantially higher for obese people than those in the healthy weight range at each level of reflux frequency. The co-occurrence of obesity and frequent reflux symptoms (OR = 5.8, 95% CI 3.3 to 10.1) led to considerably higher risks than either obesity in the absence of reflux (OR = 2.1, 95% CI 1.3 to 3.6) or reflux in the absence of obesity (OR = 3.6, 95% CI 2.0 to 6.7), but the risks were not significantly different from those expected assuming additive effects ($S = 1.3$, 95% CI 0.6 to 2.7).

Combined effects of obesity and smoking

Smokers with high cumulative exposures had significantly higher risks of oesophageal and gastro-oesophageal junction adenocarcinomas than never smokers (table 4, "Smoking overall association"). Analysis of smoking status (never, former, current) resulted in associations of similar magnitude (oesophageal adenocarcinoma: former smokers OR = 1.5, 95% 1.1 to 2.1; current smokers OR = 2.3, 95% CI 1.5 to 3.5; gastro-oesophageal adenocarcinoma: former smokers OR = 1.9, 95% CI 1.4 to 2.6; current smokers OR = 4.3, 95% CI 3.0 to 6.1). For adenocarcinomas of the oesophagus, risk estimates for cumulative smoking history were only minimally attenuated after further adjusting for smoking status, whereas for adenocarcinomas of the gastro-oesophageal junction, there was modest attenuation (not shown). After reclassifying participants according to BMI and their smoking history, we found risks of adenocarcinomas of the oesophagus increased monotonically with BMI among never smokers. There was no evidence that combined exposure to obesity and heavy smoking led to higher or lower risks than predicted under an additive model ($S = 0.6$, 95% CI 0.3 to 1.4). Generally similar patterns were observed for adenocarcinomas of the gastro-oesophageal junction.

DISCUSSION

We found consistently higher risks of adenocarcinomas of the oesophagus and gastro-oesophageal junction among obese people than among those in the healthy weight range. Our data suggest that the risks associated with obesity are independent of the risks associated with symptoms of gastro-oesophageal reflux and other factors. Indeed, these epidemiological data might be cautiously interpreted as evidence for synergistic activity between high body mass and gastro-oesophageal reflux in promoting adenocarcinomas of the oesophagus, and to a lesser extent, the gastro-oesophageal junction.

Obesity has previously been shown to be a determinant of gastro-oesophageal reflux in many studies,[9–11 13 14] although not

all.[28] Obesity has also been associated with Barrett's oesophagus[29] and oesophageal adenocarcinoma.[16–20] A pathway through which the effect of obesity is mediated by gastro-oesophageal reflux would be a parsimonious explanation for the observed association between obesity and oesophageal adenocarcinoma.[15] Our finding that risks of adenocarcinoma were only modestly attenuated after including the effects of gastro-oesophageal reflux argues against this simple model, however. Moreover, we and others[16 19] have found obesity to be associated with significantly increased risks of oesophageal adenocarcinoma even among people who had never experienced symptoms of reflux. Because the risks of combined exposure to high BMI and frequent symptoms of gastro-oesophageal reflux were significantly higher than the sum of the independent risks, we speculate that obesity plays a further part in the development of oesophageal adenocarcinoma, over and above its likely role in promoting reflux. Earlier analyses have suggested higher risks of BMI in the presence of reflux, although neither of those studies formally assessed biological interactions.[18 30]

Smoking significantly increased the risk of oesophageal and junctional adenocarcinomas, but there was no evidence of an interaction with body mass. Among never smokers and those with a modest smoking history, risks of both cancers were significantly higher among obese than non-obese people. However, among heavy smokers, there was no difference in risk of oesophageal adenocarcinoma between healthy, overweight or obese people. Qualitatively similar observations with stronger effects of BMI among never smokers have been made previously.[18] This pattern of association might be partly explained by the effects of smoking on lowering body mass.[31 32]

Our study had strengths and weaknesses. The large samples of patients newly diagnosed with oesophageal and gastro-oesophageal cancer were prospectively identified and ascertained from the Australian population, and were compared with a large control series sampled from a population register. Neither participants nor interviewers were informed of the study hypotheses, minimising the possibility of biased recall. Objective measures of adiposity (such as the waist–hip ratio or waist circumference) are generally preferred to self-reports of weight and height for studies investigating causal associations.[14] Such measures are not appropriate for case–control studies where cancer is the end point, however, because case participants in such studies have typically lost considerable amounts of body mass in the period preceding their diagnosis, and often also as a consequence of treatment.

Similarly, we had no reliable measures of past infection with *Helicobacter pylori*, which has been negatively associated with gastro-oesophageal reflux and oesophageal adenocarcinoma[33] and has been implicated in suppressing appetite and body weight[34] and thus might potentially confound the association between BMI and oesophageal adenocarcinoma. We did ask participants whether they had ever been clinically diagnosed with this infection, noting that this would require a blood or breath test, or endoscopy. In our sample, the self-reported prevalence of clinical diagnosis for *H pylori* infection was 6.3% among controls, 6.8% among oesophageal adenocarcinoma cases and 8.5% among gastro-oesophageal adenocarcinoma cases, considerably lower than the prevalence estimates of 30–40% reported in recent population-based serological studies of asymptomatic Australian adults.[35 36] Adjustment for this self-reported measure made no difference to the risk estimates, and was not included in the final models.

Although we cannot entirely exclude recall bias as a source of error, several observations argue against differential reporting of BMI as an explanation for our findings. First, risk estimates for each measure of BMI were consistently higher for adenocarcinomas of the oesophagus than the gastro-oesophageal junction, a specific pattern of risk unlikely to be due to biased recall by study participants. Second, the overall association was specific for adenocarcinomas but not SCCs (data not shown). This suggests that the effect of BMI is not simply due to over-reporting of body mass by all patients with "oesophageal cancer".

Our participation rates were less than ideal, leading to concerns about selection bias. The age and sex distribution of the participating cases was similar to the distribution of all potentially eligible cases notified to the Australian national cancer statistics clearing house (2002); however, further details of non-participating cases were not available from registries owing to privacy laws. Risk estimates would be biased upwards if the prevalence of the key exposures of interest (namely obesity and gastro-oesophageal reflux) was lower among our control group than the target population. We dealt with this problem by comparing the BMI distribution in our control series with those reported by the Australian National Health Survey (NHS) conducted in 2004, a representative survey of the Australian adult population. BMI was similarly distributed among our controls and NHS participants. Moreover, we compared our study BMI risk estimates with those derived using models that imputed the NHS BMI distributions onto our control series (manuscript under review). Risk estimates for the effect of BMI were essentially unchanged by this procedure, suggesting no appreciable bias due to a selected control sample.

The prevalence of at least weekly symptoms of reflux among our population sample of controls (12% among men and 11% among women) was similar to prevalence estimates from other population surveys in Australia,[37] the UK[9] and Sweden.[38] We therefore consider the likelihood of biased selection on the basis of this symptom to be no greater than for previous studies.

Assuming our findings reflect true causal associations, the question arises as to how obesity might cause oesophageal adenocarcinoma. Increased reflux frequency remains one plausible mechanism, since high BMI and anthropometric measures of obesity have been associated with frequent reflux symptoms,[8 9 12 14 39] as well as with asymptomatic acid reflux and erosive oesophagitis.[40 41] Central adiposity is postulated to promote acid reflux, possibly through increased intra-abdominal pressure,[42] although data in support of a mechanical effect of obesity are weak.[43] Other mechanisms through which obesity might induce reflux have also been advanced.[44] Arguing against the notion that obesity increases the risk of oesophageal adenocarcinoma simply by inducing reflux was our finding that the risk estimates associated with BMI were only modestly attenuated by including measures of symptomatic reflux in regression models. Moreover, we found that obesity remained a highly significant risk factor even among people with no reported history of reflux.

Might other factors have a role? Recent interest has focused on the endocrine effects of adipose tissue and its potential role in carcinogenesis. With obesity, there is generally an increase in insulin production, which in turn leads to the synthesis of insulin-like growth factor (IGF-I). Both these hormones can stimulate cell proliferation and inhibit apoptosis—conditions which are conducive to cancer development and for which there is some evidence of an effect.[45]

Fat cells also produce peptide hormones such as leptin, adiponectin and resistin, collectively known as adipocytokines, some of which have been shown to have mitogenic and

angiogenic effects in a variety of tissues including the oesophagus.[46 47] The role of leptin warrants further scrutiny, as its expression is upregulated in wounds[48] and it has been shown to promote repair of gastric ulcers[49] and skin wound when applied systemically and topically.[50] One might speculate that the higher levels of leptin among the obese may promote proliferation of oesophageal epithelial cells, particularly when inflamed. Whether adipocytokines enhance proliferation in oesophageal tissues in the absence of inflammation is not known, although such a mechanism would explain our finding of higher risks of oesophageal adenocarcinoma cancer among obese people without symptoms of reflux. An alternative explanation is that obese people have higher rates of asymptomatic reflux and oesophagitis, and that this phenomenon underlies the observed association.

In summary, these data confirm that obesity independently increases the risk of adenocarcinomas of the oesophagus, and to a lesser extent, the gastro-oesophageal junction. From a clinical perspective, these data raise the prospect that patients with obesity and frequent symptomatic reflux are at especially increased risk of adenocarcinoma. Understanding the mechanisms through which these exposures might cause cancer is the focus of our continuing research.

Acknowledgements: We thank Harish Babu MD for his assistance with pathology abstractions. This study was supported by the Queensland Cancer Fund and the National Health and Medical Research Council (NHMRC) of Australia (Program No 199600). David Whiteman and Penelope Webb are supported by senior research fellowships from the National Health and Medical Research Council of Australia and Queensland Cancer Fund, respectively. Shahram Sadeghi and Nirmala Pandeya are supported by PhD scholarships from the Ministry of Health and Medical Education of IR Iran and the National Health and Medical Research Council of Australia, respectively. The funding bodies played no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or preparation, review or approval of the manuscript.

Australian Capital Territory: Charles Mosse FRACS, Noel Tait FRACS
New South Wales: Chris Bambach FRACS, Andrew Biankan FRACS, Roy Brancatisano FRACS, Max Coleman FRACS, Michael Cox FRACS, Stephen Deane FRACS, Gregory L. Falk FRACS, James Gallagher FRACS, Mike Hollands FRACS, Tom Hugh FRACS, David Hunt FRACS, John Jorgensen FRACS, Christopher Martin FRACS, Mark Richardson FRACS, Garrett Smith FRACS, Ross Smith FRACS, David Storey FRACS
Queensland: John Avramovic FRACS, John Croese FRACP, Justin D'Arcy FRACS, Stephen Fairley FRACP, John Hansen FRACS, John Masson FRACP, Les Nathanson FRACS, Barry O'Loughlin FRACS, Leigh Rutherford FRACS, Richard Turner FRACS, Morgan Windsor FRACS
South Australia: Justin Bessell FRACS, Peter Devitt FRACS, Glyn Jamieson FRACS, David Watson FRACS
Victoria: Stephen Blamey FRACS, Alex Boussioutas FRACP, Richard Cade FRACS, Gary Crosthwaite FRACS, Ian Faragher FRACS, John Gribbin FRACS, Geoff Hebbard FRACP, George Kiroff FRACS, Bruce Mann FRACS, Bob Millar FRACS, Paul O'Brien FRACS, Robert Thomas FRACS, Simon Wood FRACS
Western Australia: Steve Archer FRACS, Kingsley Faulkner FRACS, Jeff Hamdorf FRACS

Competing interests: None.

REFERENCES

1. **Blot WJ,** Devesa SS, Kneller RW, *et al*. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991;**265**:1287–9.
2. **Lord RV,** Law MG, Ward RL, *et al*. Rising incidence of oesophageal adenocarcinoma in men in Australia. *J Gastroenterol Hepatol* 1998;**13**:356–62.
3. **Wayman J,** Forman D, Griffin SM. Monitoring the changing pattern of esophagogastric cancer: data from a UK regional cancer registry. *Cancer Causes Control* 2001;**12**:943–9.
4. **Australian Institute of Health and Welfare**. National Cancer Statistics Clearing House, 2006.
5. **Pohl H,** Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst* 2005;**97**:142–6.
6. **Chow WH,** Finkle WD, McLaughlin JK, *et al*. The relation of gastroesophageal reflux disease and its treatment to adenocarcinomas of the esophagus and gastric cardia. *JAMA* 1995;**274**:474–7.
7. **Lagergren J,** Bergstrom R, Lindgren A, *et al*. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N Engl J Med* 1999;**340**:825–31.
8. **Nilsson M,** Johnsen R, Ye W, *et al*. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. *JAMA* 2003;**290**:66–72.
9. **Murray L,** Johnston B, Lane A, *et al*. Relationship between body mass and gastro-oesophageal reflux symptoms: the Bristol Helicobacter Project. *Int J Epidemiol* 2003;**32**:645–50.
10. **Hampel H,** Abraham NS, El-Serag HB. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann Intern Med* 2005;**143**:199–211.
11. **El-Serag HB,** Graham DY, Satia JA, *et al*. Obesity is an independent risk factor for GERD symptoms and erosive esophagitis. *Am J Gastroenterol* 2005;**100**:1243–50.
12. **Jacobson BC,** Somers SC, Fuchs CS, *et al*. Body-mass index and symptoms of gastroesophageal reflux in women. *N Engl J Med* 2006;**354**:2340–8.
13. **El-Serag HB,** Ergun GA, Pandolfino J, *et al*. Obesity increases oesophageal acid exposure. *Gut* 2007;**56**:749–55.
14. **Corley DA,** Kubo A, Zhao W. Abdominal obesity, ethnicity and gastro-oesophageal reflux symptoms. *Gut* 2007;**56**:756–62.
15. **Lagergren J.** Controversies surrounding body mass, reflux, and risk of oesophageal adenocarcinoma. *Lancet Oncol* 2006;**7**:347–9.
16. **Brown LM,** Swanson CA, Gridley G, *et al*. Adenocarcinoma of the esophagus: role of obesity and diet. *J Natl Cancer Inst* 1995;**87**:104–9.
17. **Vaughan TL,** Davis S, Kristal A, *et al*. Obesity, alcohol, and tobacco as risk factors for cancers of the esophagus and gastric cardia: adenocarcinoma versus squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev* 1995;**4**:85–92.
18. **Chow WH,** Blot WJ, Vaughan TL, *et al*. Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst* 1998;**90**:150–5.
19. **Lagergren J,** Bergstrom R, Nyren O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. *Ann Intern Med* 1999;**130**:883–90.
20. **Kubo A,** Corley DA. Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006;**15**:872–8.
21. **Adami HO,** Trichopoulos D. Obesity and mortality from cancer. *N Engl J Med* 2003;**348**:1623–4.
22. **Calle EE,** Rodriguez C, Walker-Thurmond K, *et al*. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003;**348**:1625–38.
23. **Calle EE,** Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004;**4**:579–91.
24. **Jordan SJ,** Green AC, Whiteman DC, *et al*. Risk factors for benign serous and mucinous epithelial ovarian tumors. *Obstet Gynecol* 2007;**109**:647–54.
25. **Spechler SJ,** Dixon MF, Genta R, *et al*. Adenocarcinoma of the oesophago-gastric junction. In: Hamilton SR, Aaltonen LA, eds. *Pathology and genetics tumours of the digestive system. WHO classification of tumours*. Vol 2. UK: Lyon IARC Press, 2000.
26. **Rothman KJ.** *Modern epidemiology*. 1st ed. Boston: Little Brown and Co, 1986.
27. **Andersson T,** Alfredsson L, Kallberg H, *et al*. Calculating measures of biological interaction. *Eur J Epidemiol* 2005;**20**:575–9.
28. **Lagergren J,** Bergstrom R, Nyren O. No relation between body mass and gastro-oesophageal reflux symptoms in a Swedish population based study. *Gut* 2000;**47**:26–9.
29. **Smith KJ,** O'Brien SM, Smithers BM, *et al*. Interactions among smoking, obesity, and symptoms of acid reflux in Barrett's esophagus. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:2481–6.
30. **Lagergren J,** Ye W, Bergstrom R, *et al*. Utility of endoscopic screening for upper gastrointestinal adenocarcinoma. *JAMA* 2000;**284**:961–2.
31. **Akbartabartoori M,** Lean ME, Hankey CR. Relationships between cigarette smoking, body size and body shape. *Int J Obes (Lond)* 2005;**29**:236–43.
32. **Lissner L,** Bengtsson C, Lapidus L, *et al*. Smoking initiation and cessation in relation to body fat distribution based on data from a study of Swedish women. *Am J Public Health* 1992;**82**:273–5.
33. **Chow WH,** Blaser MJ, Blot WJ, *et al*. An inverse relation between cagA+ strains of Helicobacter pylori infection and risk of esophageal and gastric cardia adenocarcinoma. *Cancer Res* 1998;**58**:588–90.
34. **Loffeld RJ.** Helicobacter pylori, obesity and gastro-oesophageal reflux disease. Is there a relation? A personal view. *Neth J Med* 2005;**63**:344–7.
35. **Lin SK,** Lambert JR, Nicholson L, *et al*. Prevalence of Helicobacter pylori in a representative Anglo-Celtic population of urban Melbourne. *J Gastroenterol Hepatol* 1998;**13**:505–10.
36. **Robertson MS,** Cade JF, Savoia HF, *et al*. Helicobacter pylori infection in the Australian community: current prevalence and lack of association with ABO blood groups. *Intern Med J* 2003;**33**:163–7.
37. **Talley NJ,** Quan C, Jones MP, *et al*. Association of upper and lower gastrointestinal tract symptoms with body mass index in an Australian cohort. *Neurogastroenterol Motil* 2004;**16**:413–9.
38. **Nilsson M,** Johnsen R, Ye W, *et al*. Prevalence of gastro-oesophageal reflux symptoms and the influence of age and sex. *Scand J Gastroenterol* 2004;**39**:1040–5.
39. **Wu AH,** Tseng CC, Bernstein L. Hiatal hernia, reflux symptoms, body size, and risk of esophageal and gastric adenocarcinoma. *Cancer* 2003;**98**:940–8.
40. **Ortiz V,** Ponce M, Fernandez A, *et al*. Value of heartburn for diagnosing gastroesophageal reflux disease in severely obese patients. *Obesity* 2006;**14**:696–700.

41. **Ronkainen J,** Aro P, Storskrubb T, *et al*. High prevalence of gastroesophageal reflux symptoms and esophagitis with or without symptoms in the general adult Swedish population: a Kalixanda study report. *Scand J Gastroenterol* 2005;**40**:275–85.
42. **Nilsson M,** Lagergren J. The relation between body mass and gastro-oesophageal reflux. *Best Pract Res Clin Gastroenterol* 2004;**18**:1117–23.
43. **El-Serag HB,** Tran T, Richardson P, *et al*. Anthropometric correlates of intragastric pressure. *Scand J Gastroenterol* 2006;**41**:887–91.
44. **Nilsson M,** Lundegardh G, Carling L, *et al*. Body mass and reflux oesophagitis: an oestrogen-dependent association? *Scand J Gastroenterol* 2002;**37**:626–30.
45. **Renehan AG,** Zwahlen M, Minder C, *et al*. Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet* 2004;**363**:1346–53.
46. **Somasundar P,** Riggs D, Jackson B, *et al*. Leptin stimulates esophageal adenocarcinoma growth by nonapoptotic mechanisms. *Am J Surg* 2003;**186**:575–8.
47. **Ogunwobi O,** Mutungi G, Beales IL. Leptin stimulates proliferation and inhibits apoptosis in Barrett's esophageal adenocarcinoma cells by cyclooxygenase-2-dependent, prostaglandin-E2-mediated transactivation of the epidermal growth factor receptor and c-Jun NH2-terminal kinase activation. *Endocrinology* 2006;**147**:4505–16.
48. **Murad A,** Nath AK, Cha ST, *et al*. Leptin is an autocrine/paracrine regulator of wound healing. *FASEB J* 2003;**17**:1895–7.
49. **Konturek PC,** Brzozowski T, Sulekova Z, *et al*. Role of leptin in ulcer healing. *Eur J Pharmacol* 2001;**414**:87–97.
50. **Ring BD,** Scully S, Davis CR, *et al*. Systemically and topically administered leptin both accelerate wound healing in diabetic ob/ob mice. *Endocrinology* 2000;**141**:446–9.

BENIGN OESOPHAGEAL DISEASES

During the course of the evolution of minimally invasive surgery and endoscopy I pioneered techniques which were utilised extensively to improve operative procedures and techniques of the oesophagus, both within the thoracic cavity and the abdominal cavity. Multiple procedures previously done by laparotomy or thoracotomy were managed by laparoscopy and endoscopy much to the patient's advantage in speed of recovery and diminished discomfort. Much of this work was reported at international meetings and been published predominantly in abstract form. I was asked to give multiple expositions and video presentations. The previous chapters on development of laparoscopic fundoplication and laparoscopic repair of giant hiatus hernias are a subgroup of the overall category of oesophageal disease. In this way the common theme of my pursuit of the physiological surgical management of oesophageal disease and pioneering laparoscopy was combined.

References:

1. Falk GL. Risk awareness for proton pump inhibition: Necessitates review of recommendations in anti-reflux disease. Surgeon. 2020;18(3):189-90.

2. Falk GL, Little SC. Gastro-oesophageal fistula in an achalasia patient following myotomy as anunusual cause of heartburn. Ann R Coll Surg Engl. 2019;101(2):e35-e7.

3. D'Nètto TJ, Falk GL, Little SC. An improved laparoscopic technique for myotomy and fundoplication in patients with achalasia. European Surgery. 2018;50(1):4-7.

4. Furtado RV, Beasley WF, Mastrocostas K, Falk GL. Oesophageal haematoma masquerading as cardiac ischaemia. ANZ J Surg. 2015;85(10):790-1.

6. Richardson M, Harrison, R.I., Falk, G.L. Early symptomatic results of laparoscopic Heller's Myotomy and fundoplication for Achalasia. Le Journal de Coelio-Chirurgie. 2000;33:80-3.

THE SURGEON 18 (2020) 189–190

Correspondence: Letter to the Editor

Risk awareness for proton pump inhibition: Necessitates review of recommendations in anti-reflux disease

Keywords:
Proton pump inhibitors
Reflux disease
Oesophagitis
Chronic PPI use
H2 antagonists

To the Editor,

Proton pump inhibition (PPI) has been greatly utilised in treatment of reflux disease symptoms and oesophagitis. It has additionally been used extensively for patients with atypical reflux symptoms such as reflux cough. Reflux disease has been reported as variably affecting 10%–20% of a western population[1] and chronic cough much of which has been attributed to reflux disease, 5%–41%.[2] It has been reported 50% of patients on chronic PPI usage have no obvious indication for such treatment.[3,4] The drugs of course are utilised for other indications including dyspepsia, ulceration healing, ulcer prophylaxis and indistinct gastrointestinal symptoms frequently.

Extensive usage has been highly expensive for the health funding and has been predicated upon a belief that PPI usage was relatively safe. Recent studies[4,5] have called this somewhat into question. One study noted an all-cause increase in mortality in patients treated chronically with PPI, and a further noted an increased rate of gastric carcinoma in a large series of patients managed in Hong Kong following *Helicobacter pylori* eradication treatment[5] and then continued PPI prescription (63,396 patients). This was a database study and so can only be considered indicative rather than absolute although careful statistical analysis was performed. A recent systematic review[6] shows a little evidence, however cannot be conclusive regarding the increased rate of gastric cancer. Gracie et al. in review have pointed out the conflicting evidence of previous meta-analysis.[7]

Mechanisms have long been recognised in the consideration of the development of gastric cancer due to iatrogenic acid reduction. Correa 2011 has described an inexplicable increase in younger patients in the United States developing gastric cancer for unknown cause.[8] Several other previous studies have not shown a risk attached to PPI usage.[9]

The evident mortality found in the BMJ cohort[4] of American veterans (349 312 patients) could be confounded by the increased age of the PPI patient group however the effect was even apparent in relatively recent chronic use of PPI and there appeared to be a time dependent relationship. This effect was not seen with H2 antagonists. Attribution of cause of death was not possible in this study. Multiple and adverse effects of PPI have been identified or hypothesised including osteoporosis, hip fracture, cardiovascular disease, possibly dementia, rates of *Clostridium difficile* increase, gastroenteritis, associated renal disease, and recurrent pulmonary infection. Concerning physiological and biochemical changes are identified including telomere shortening, reduction in oxidative stress mechanisms, impairment of proto stasis, endothelial dysfunction and increased human endothelial cell senescence. Concern is increasingly being raised in Australia.

In non-United States western population anti-reflux surgery has largely been in PPI resistance disease. The SAGES guidelines currently indicate anti-reflux surgery as an alternative to PPI in the United States.[10] Concern has been raised in Australia about substantial over prescribing of PPI.[11]

There appears to be an increasing body of evidence indicating a probable risk associated with long-term PPI usage. This awaits further confirmation, but the publication of these recent articles is likely to stimulate frenetic activity. In the meantime re-consideration of long-term PPI usage in the young to middle-aged patient where alternative therapies exist it is required. Indications for anti-reflux surgery require revision in countries outside United States and patients need more complete information in their management, which increasingly is a balance of risks. Poorly indicated use of PPI should stop.

Conflicts of interest

Author declares no conflict of interest.

REFERENCES

1. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2005;**54**(5):710–7.
2. Irwin RS. Chronic cough due to gastroesophageal reflux disease: ACCP evidence-based clinical practice guidelines. *Chest* 2006;**129**(1 Suppl):80s–94s.
3. Othman F, Card TR, Crooks CJ. Proton pump inhibitor prescribing patterns in the UK: a primary care database study. *Pharmacoepidemiol Drug Saf* 2016;**25**(9):1079–87.
4. Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States veterans. *BMJ Open* 2017;**7**(6):e015735.

5. Cheung KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. *Gut* 2017;**67**(1):28–35.
6. Tran-Duy A, Spaetgens B, Hoes AW, de Wit NJ, Stehouwer CD. Use of proton pump inhibitors and risks of fundic gland polyps and gastric cancer: systematic review and meta-analysis. *Clin Gastroenterol Hepatol – Off Clin Pract J Am Gastroenterol Assoc* 2016;**14**(12):1706–19. e5.
7. Gracie DJ, Ford AC. The possible risks of proton pump inhibitors. *Med J Aust* 2016;**205**(7):292–3.
8. Correa P. Gastric cancer: two epidemics? *Dig Dis Sci* 2011;**56**(5): 1585–6. author reply 6.
9. Klinkenberg-Knol EC, Festen HP, Jansen JB, Lamers CB, Nelis F, Snel P, et al. Long-term treatment with omeprazole for refractory reflux esophagitis: efficacy and safety. *Ann Intern Med* 1994;**121**(3):161–7.
10. Guidelines for surgical treatment of gastroesophageal reflux disease (GERD). Society of American Gastrointestinal Endoscopic Surgeons (SAGES). *Surg Endosc* 1998;**12**(2):186–8.
11. Weekes LM. Proton pump inhibitors: too much of a good thing? *Med J Aust* 2015;**202**(9):464.

Gregory L. Falk*
Sydney Heartburn Clinic, Lindfield, NSW, 2070, Australia
CI/A Professor of Surgery, University of Sydney, Sydney, NSW, Australia
Concord Repatriation Hospital, Concord, NSW, Australia

*Suite 29, 12 Tryon Road, Lindfield, NSW, 2070, Australia. Fax: +612 9416 2907.
E-mail address: sydney.heartburn@gmail.com

Available online 11 October 2019

1479-666X/$ – see front matter

https://doi.org/10.1016/j.surge.2019.09.001

Royal College of Surgeons
ADVANCING SURGICAL CARE

ONLINE CASE REPORT

Ann R Coll Surg Engl 2019; **101:** e35–e37
doi 10.1308/rcsann.2018.0179

Gastro-oesophageal fistula in an achalasia patient following myotomy as an unusual cause of heartburn

GL Falk, SC Little

Sydney Heartburn Clinic, Lindfield, Australia

ABSTRACT

We report a case of delayed presentation of a gastro-oesophageal fistula following a Heller myotomy and anterior fundoplication for achalasia in a 28-year-old man. After a period of symptom resolution following initial operation, dysphagia and severe heartburn commenced temporarily, related to non-steroidal anti-inflammatory drug (NSAID) use. Endoscopy demonstrated a secondary opening in the lower oesophagus and a barium swallow showed an oesophageal fistula to the stomach. Currently, reasonable symptom control has been obtained on double dose pantoprazole. Barium study best demonstrated the abnormality. NSAIDs should possibly be avoided in cases of severe dysmotility of the oesophagus.

KEYWORDS

Fundoplication – Heller myotomy – Non-steroidal anti-inflammatory drugs – Oesophageal achalasia – Oesophageal fistula

Accepted 10 September 2018

CORRESPONDENCE TO

Gregory Falk, E: sydney.heartburn@gmail.com

Gastro-oesophageal fistula following cardio-oesophageal junction surgery is an uncommon phenomenon. A clear pathway for management has not been identified because of its relative rarity. We report a case occurring following a Heller myotomy and fundoplication in an adult, whose symptoms are currently managed medically. This situation was made more complex by the myotomy communicating with the stomach and peristaltic dysfunction of achalasia.

Case history

A 28-year-old fit man presented to our service with intractable heartburn, increasing dysphagia and regurgitation to the throat of several months' duration. Two years earlier, he had undergone a laparoscopic Heller myotomy and anterior fundoplication for type 1 achalasia in another hospital.

Preoperative manometry had confirmed a poorly relaxing lower oesophageal sphincter pressure with a midexpiratory resting value of 35mmHg and fluctuating resting pressure. Partial relaxation to 15mm on swallow was seen and there was complete absence of any peristaltic activity. A preoperative barium study confirmed a bird's beak abnormality, absent peristalsis, a column of barium during swallow and mild oesophageal dilation. A laparoscopic anterior myotomy and anterior hemifundoplication was performed without issue. Postoperative recovery was uneventful and antisecretory therapy was continued indefinitely.

Two years following surgery, non-steroidal anti-inflammatory drugs (NSAIDs) were given for treatment of ankylosing spondylitis. This was not tolerated owing to a severe increase in heartburn. Endoscopy performed elsewhere demonstrated grade 3 oesophagitis and a lateral oesophageal opening just above the sphincter (Fig 1). Twice daily treatment with 40mg of pantoprazole was instituted with partial reduction in heartburn symptomatology but unchanging dysphagia. NSAIDs were ceased as a result of the aggravation of heartburn symptomatology and the clinical symptoms were incompletely resolved.

The clinical picture was considered that of a gastroesophageal fistula secondary to surgery for achalasia, based on review of the endoscopic photographs, and a barium study was undertaken to confirm this impression (Fig 2). Appearances were those of a fistula between the anterior fundoplication and the oesophagus several millimetres above the lower oesophageal sphincter zone. The worsening of the heartburn with the NSAIDs was considered to be due to the ulcerogenic effects of the medication.

The patient avoided NSAIDs and undertook treatment of the ankylosing spondylitis with tumour necrosis factor medications with reasonable symptomatic outcome of musculoskeletal discomfort. Reflux symptoms became controlled on double dose pantoprazole.

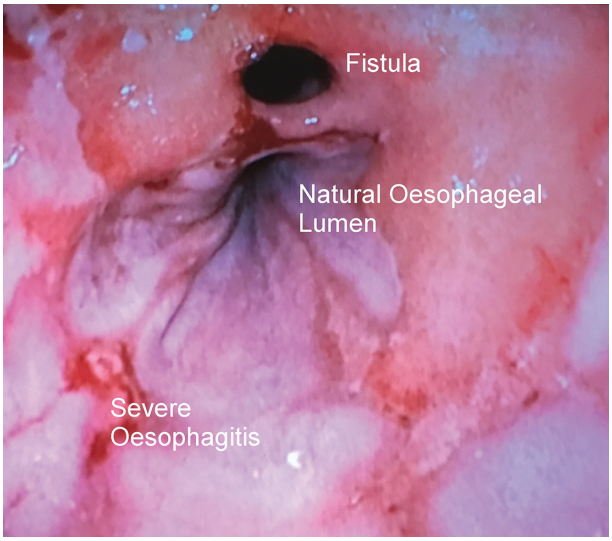


Figure 1 Endoscopic view of cardio-oesophageal junction with oesophageal defect

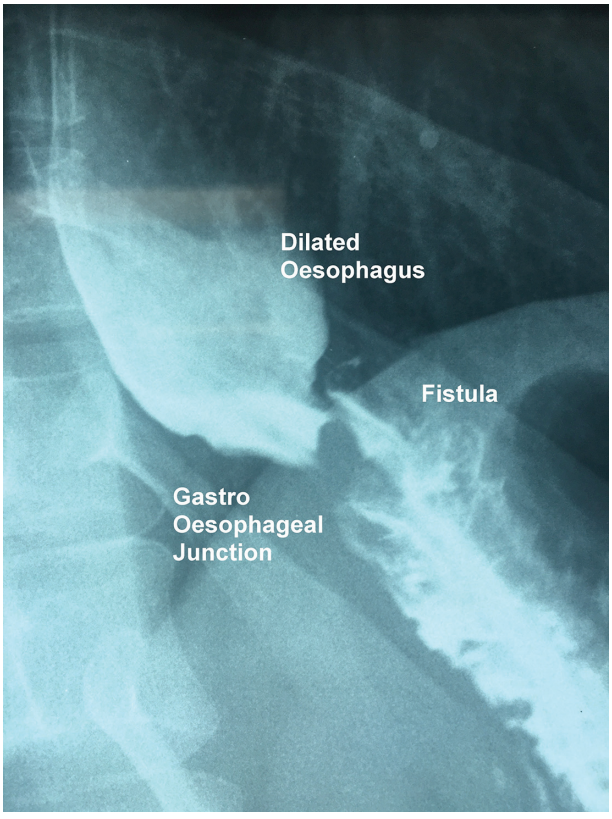


Figure 2 View of fistula and gastro-oesophageal junction on barium swallow

To date, no surgical or endoscopic therapy has been recommended as symptoms are tolerable on medical treatment. This situation has been stable for 18 months. While surgical treatment for this severe oesophagitis would seem advisable to prevent the development of an oesophageal stricture or Barrett's oesophagus, it seems feasible that surgery could be delayed. The patient has been advised that worsening symptomatology (especially dysphagia) would prompt definitive action. Regular endoscopic review is scheduled.

Discussion

The patient presented with typical worsening reflux symptoms with proximal symptoms of regurgitation. This reflected the uncontrolled reflux of fluid through the fistula, avoiding the antireflux mechanism of the partial fundoplication. Worsening dysphagia was thought to be due to oesophagitis as it became less troublesome after an increased dose of pantoprazole. Such severe reflux may cause nocturnal choking, especially inhalation or laryngospasm. This was not evident in our case.

This situation appears to be an uncommon delayed consequence of previous cardio-oesophageal junction surgery. The wall of the oesophagus was necessarily attenuated as a result of the myotomy and an anterior partial fundoplication allowed communication through the myotomy to the gastric lumen within the fundoplication. Several aetiological factors may have led to this situation, including damage during primary surgery, infection, ulceration secondary to reflux or a suture transgressing mucosal boundaries. The corrosive effect of NSAIDs may have been aetiological, with dissolution of a poorly transmitted pill at the site of the fistula causing local transmural inflammation. The temporal relation with NSAID use is suggestive as so it would seem prudent to avoid oral NSAIDs in cases of poor oesophageal motility. All of these aetiological possibilities remain speculative. A literature search did not reveal any similar cases following a Heller myotomy.

Endoscopy had raised the suspicion of a fistula but did not delineate a passage into the stomach although this was suspected given the history and severe oesophagitis. A barium study, however, confirmed the fistulous track definitively. On this basis, such a study would be recommended in the future. It would seem that a barium study will allow best anatomical assessment.

Tafen *et al* described 15 cases of oesophagogastric fistula, not all of which were associated with previous fundoplication.[1] A few papers show association with fundoplication.[2,3] There are reports of other diseases, such as persistent peptic ulceration and neoplasia, which may also cause this phenomenon.[4] Our group has published a series of gastro-oesophageal fistula secondary to fundoplication performed using a polytetrafluoroethylene (PTFE) pledget.[5] Multiple cases characterised by severe epigastric pain ultimately resulted in gastro-oesophageal luminal penetration of PTFE and its removal by endoscopy with pain relief.

Conclusions

There have been no reports of medical management successfully repairing a gastro-oesophageal fistula following fundoplication. Multiple cases have temporarily had symptomatic relief from antisecretory therapy, as is the case for our patient currently. This seems especially helpful in the paediatric population. It does, however, appear that surgical intervention (either endoscopic, laparoscopic or open) will be the only ultimate form of cure.

References

1. Tafen M, Tehrani N, Anoushiravani AA *et al*. Esophagogastric fistula complicating Nissen fundoplication. *J Ped Surg Case Rep* 2016; **10**: 14–16.
2. Raymond JI, Khan AH, Cain LR, Ramin JE. Multiple esophagogastric fistulas resulting from reflux esophagitis. *Am J Gastroenterol* 1980; **73**: 430–433.
3. Fleming JL, DiMagno EP. Double lumen esophagus: presentation of esophagogastric fistula, a rare complication of fundoplication. *Dig Dis Sci* 1986; **31**: 106–108.
4. Mullen JT, Burke EL, Diamond AB. Esophagogastric fistula. A complication of combined operations for esophageal disease. *Arch Surg* 1975; **110**: 826–828.
5. Dally E, Falk GL. Teflon pledget reinforced fundoplication causes symptomatic gastric and esophageal lumenal penetration. *Am J Surg* 2004; **187**: 226–229.

short communication

Eur Surg (2018) 50:4–7
https://doi.org/10.1007/s10353-017-0510-0

european surgery
ACA Acta Chirurgica Austriaca

An improved laparoscopic technique for myotomy and fundoplication in patients with achalasia

Trevor J. D'Netto · Gregory L. Falk · Sophia C. Little

Received: 14 August 2017 / Accepted: 14 December 2017 / Published online: 26 January 2018

Summary
Background Achalasia is preferentially treated by esophageal myotomy. We present a potentially more secure technique of myotomy and fundoplication incorporating a three-stitch cardiopexy on the right of the esophagus and a left lateral fixation at the angle of His.
Method The process of dissection, fixation and repair is described in detail using intraoperative photographs to illustrate each step.
Conclusion This technique is especially suited to achalasia patients with abnormalities of the hiatal anatomy.

This paper offers an improvement to a well-practiced technique, which is presented in significant detail. It is of particular interest as it may improve outcomes for achalasia treatment thanks to a more secure technique.

Keywords Achalasia · Laparoscopic fundoplication · Myotomy · Paraoesophageal hernia · Hiatus hernia

Introduction

Achalasia is preferentially treated by esophageal myotomy. This is currently performed by endoscopy or laparoscopy. Little difference in the outcome of the two techniques is apparent clinically.

Achalasia may occur in the presence of anatomical abnormality of the diaphragmatic crura and position of the lower esophageal sphincter. This is a relative indication for a laparoscopic approach to reconstitute the normal position of the esophagus and for re-approximation of the crura. It is expected that this technique will stabilize the myotomy/repair against later slippage.

The process of dissection, fixation, and repair is described in detail using intraoperative photographs to illustrate each step.

Preoperative diagnosis

Esophageal manometry: common cavity effect and absence of peristalsis are demonstrated in Fig. 1.

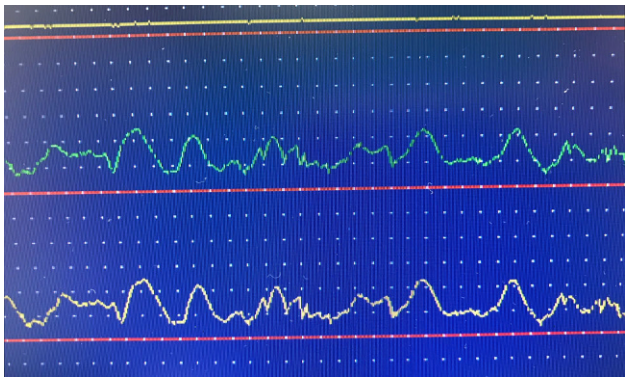


Fig. 1 Esophageal manometry demonstrating absent peristalsis and common cavity effect

T. J. D'Netto, MBBS (Hons)
Sydney Adventist Hospital, Wahroonga, NSW, Australia
dnetto@optusnet.com.au

G. L. Falk, MBBS FRACS FACS
Concord Repatriation General Hospital,
Concord, NSW, Australia

G. L. Falk, MBBS FRACS FACS (✉) · S. C. Little, B. AVBS (Hons I)
Lindfield General Surgery, 29/12 Tryon Road, Lindfield, NSW, Australia
sydney.heartburn@gmail.com

S. C. Little, B. AVBS (Hons I)
sophia.little7@gmail.com

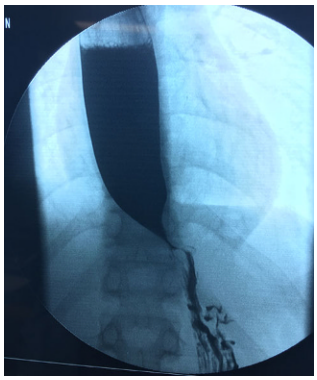


Fig. 2 Barium swallow with appearances of a standing column of fluid and a bird's beak narrowing of the oesophagus

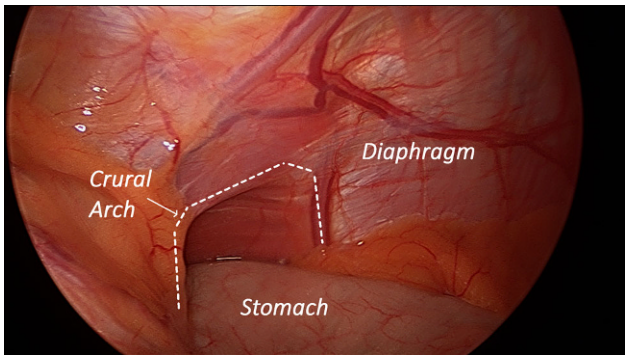


Fig. 3 Cardio-esophageal junction (COJ)

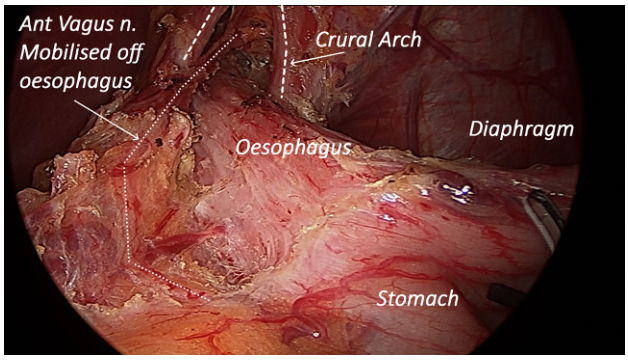


Fig. 4 Exposure of anterior vagus nerve

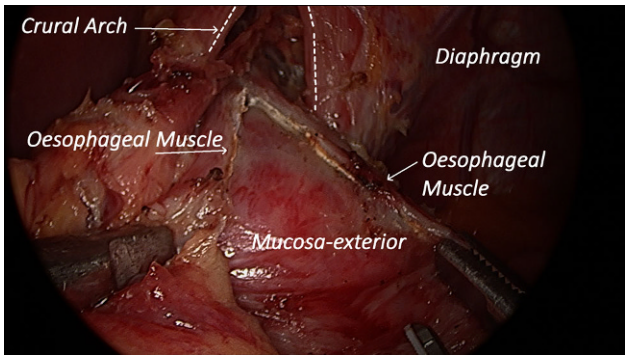


Fig. 5 Esophageal myotomy

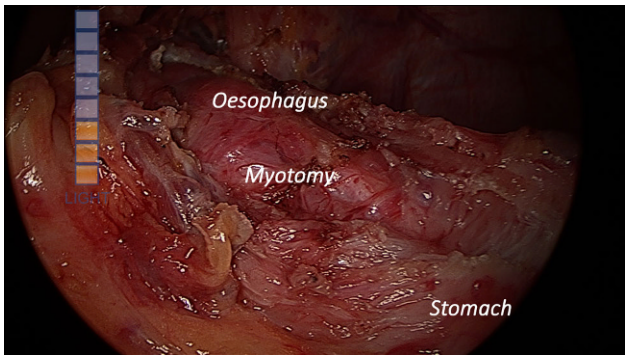


Fig. 6 Completed esophageal myotomy

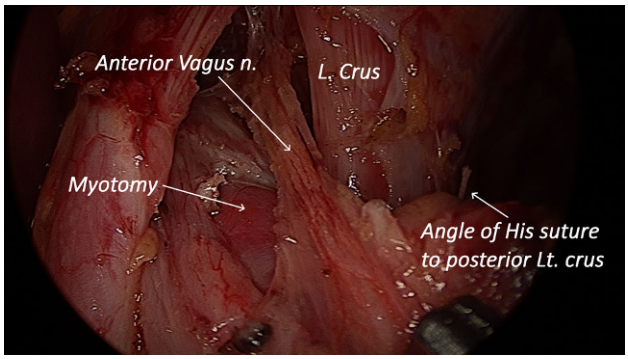


Fig. 7 Preservation of the anterior vagus nerve

Barium swallow: the classic appearances of a bird's beak and standing column of barium are shown in Fig. 2.

Method

A standard technique of five-port laparoscopy with Nathanson liver retraction is performed. A harmonic scalpel (Ethicon Endosurgery, Cincinnati, Ohio) is used for dissection. Optical entry with a 5.7- or 10-mm laparoscope is performed. The sutures are exchanged through a left upper quadrant 8-mm port.

Discussion

Technique

The cardio-esophageal junction is depicted in Fig. 3.

The cardio-esophageal junction (COJ) with a small hiatus hernia is shown in a patient with achalasia: a 32-year-old female patient with a 9-month history of dysphagia, nocturnal cough, and atypical nocturnal chest pain (Fig. 4).

The esophagus is mobilized anteriorly and laterally to allow withdrawal of the COJ into the abdomen. Posterior attachments are variably divided to allow for accurate reduction. The anterior vagus nerve is well

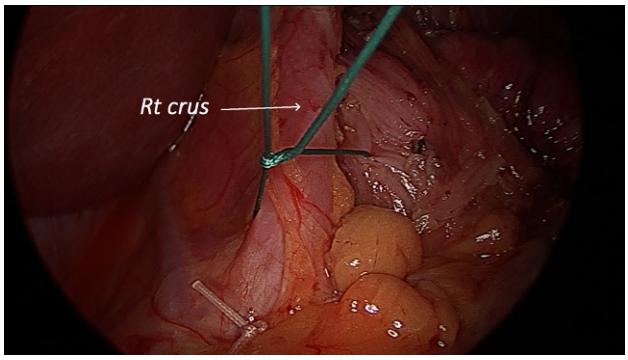


Fig. 8 Cardiopexy

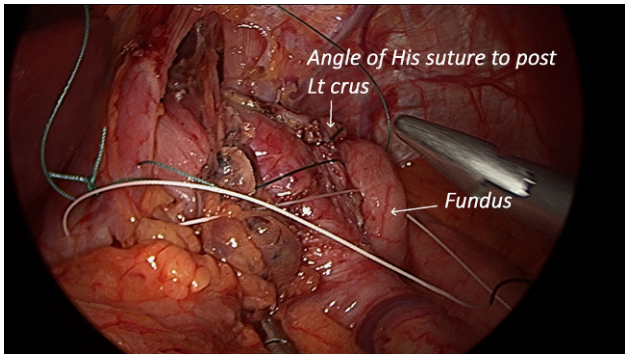


Fig. 9 Formation of the anterior fundoplication

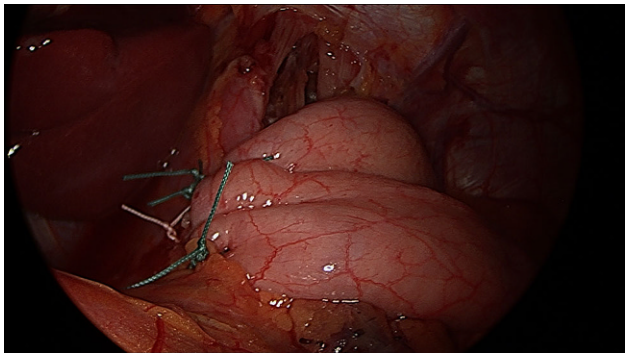


Fig. 10 Completed fundoplication

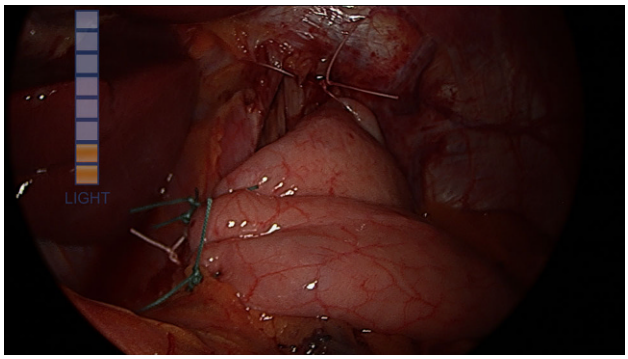


Fig. 11 Calibration of anterior arch of crura

mobilized off the esophagus to allow for later placement of cardiopexy sutures. Dissection is commenced with the harmonic scalpel laterally on the anterior fat pad and reflected to the patient's right side. This allows for excellent exposure and visualization of the anterior esophagus for myotomy (Fig. 5).

Esophageal myotomy is performed using a harmonic scalpel. The "active" blade is allowed to cool between each application to avoid thermal injury, especially to the exposed mucosa (Fig. 6).

The next step is completed myotomy onto the stomach. Intraoperative endoscopy is performed to ensure adequate division of restricting muscle fibers and easy opening of the COJ with minimal endoscopic insufflation. Perforation of the myotomy is thus excluded (Fig. 7).

The anterior vagus nerve is seen preserved in the foreground, with the myotomy now seen posteriorly. An "angle of His" suture attaching the angle of His to the posterior left crus (Fig. 8).

The first of three cardiopexy sutures through the esophageal muscle (superior) is placed to fix the esophagus inferiorly and posteriorly to the right crural pillar and median arcuate ligament. Ethibond sutures 2/0, on a 26-mm needle, pre-cut to a length of 20 cm, are utilized (Johnson and Johnson Co., N.J.). Exposure is facilitated if all sutures are placed before tying (Fig. 9).

Multiple sutures approximate the fundus to the right crus. The sutures are placed, and not tied at this stage, to facilitate excellent visualization, and then tied sequentially after all are placed (Fig. 10).

An endoscopic check is performed and the myotomy is assessed for completeness and perforation. The fundoplication sutures are tied. The endoscope remains in situ during fundoplication formation (Fig. 11).

If the hiatal opening is considered too large, the anterior crura are approximated as required. The crural opening must remain pliable after suture. The endoscope remains in situ.

Conclusion

Laparoscopic myotomy and repair of hiatus hernia are routinely utilized, and this technique has resulted in very acceptable improvement in quality of life and symptom reduction. Cardiopexy is performed to reduce reherniation risk. We found that prior to this technique some movement of the COJ occurred in patients following abdominal myotomy, and thus introduced cardiopexy as an adjunct to anterior fundoplication in an effort to reduce "slippage". Cardiopexy has been a routine technique in some centers [1].

Conflict of interest T.J. D'Netto, G.L. Falk, and S.C. Little declare that they have no competing interests.

References

1. Chino O, Makuuchi H, Ozawa S, et al. Multiple early carcinomas of the esophagus associated with achalasia treated by endoscopic submucosal dissection. Ann Cancer Res Ther. 2014;22(1):1–5.

Oesophageal haematoma masquerading as cardiac ischaemia

An 83-year-old woman was referred with a suspected, spontaneous perforation of the oesophagus.

She had presented with central chest pain radiating to the back, following a severe bout of coughing that morning. There was a past medical history of ischaemic heart disease, requiring a coronary stent and 75 mg of clopidogrel daily. Physical examination and serial electrocardiographs were normal. There was a rise in serial troponins from 22 to 44 ng/mL. Treatment was instituted, with a further 75 mg of clopidogrel and 60 mg enoxaparin, in accordance with a chest pain protocol.

A computed tomography (CT) aortogram was also performed due to a differential diagnosis of aortic dissection. This showed intramural haematoma in the oesophagus with fluid and stranding posteriorly. The post-contrast scan showed active contrast extravasation into the oesophageal lumen (Fig. 1). On initial viewing, this was felt to represent oesophageal rupture with mediastinitis. She was then urgently transferred to our tertiary upper gastrointestinal (GI) unit.

Further history obtained following transfer revealed odynophagia prior to presentation and a small volume of haematemesis following the CT scan. In order to clarify the differential diagnosis of oesophageal perforation, particularly as the patient's clinical condition did not support this diagnosis, an urgent, water-soluble contrast swallow was performed. No leak from the oesophagus was demonstrated; however, contrast was shown tracking along the peripheries, around a large central haematoma (Fig. 2). The antiplatelet and anticoagulants were stopped and a diet of clear fluids was commenced. The patient made an uneventful recovery.

With the gradual introduction of a normal diet she complained of persistent, mild dysphagia. Contrast swallow and endoscopy performed 2 weeks following discharge showed minor oesophageal mucosal changes and partial resolution of the haematoma.

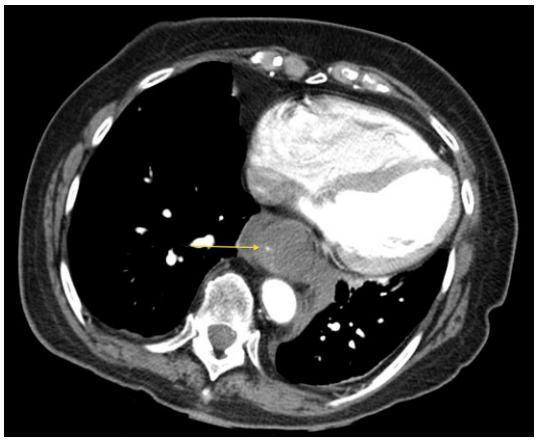


Fig. 1. This axial computed tomography angiogram demonstrates contrast extravasation within the eccentric oesophageal lesion (arrow), and a normal appearance of the thoracic aorta (which is separate to the lesion).

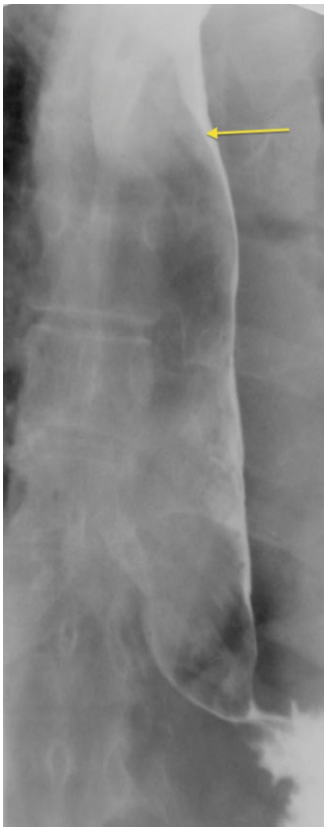


Fig. 2. A frontal single-contrast swallow demonstrates a smooth, sausage-like, eccentric filling defect (arrow) involving the posterior wall of the distal thoracic oesophagus in keeping with an intramural haematoma.

Intramural hematoma represents one of the outcomes from oesophageal wall trauma, which can vary considerably from relatively minor mucosal injuries to full-thickness perforation. It most commonly occurs in older women on anticoagulation.[1] The precipitating incident is often a change in intrathoracic pressure such as coughing, vomiting or Valsalva.[2] It can also occur secondary to trauma from ingested food (e.g. fish bones[3]) or instrumentation.[4] The natural history is resolution with conservative treatment, in most cases. A minority of patients will have persistent dysphagia.[1]

The typical radiological features are an eccentric, luminal, filling defect on contrast swallow or CT. If the mucosal breach is still patent, this will instead appear as a 'double-barrelled' oesophagus. In this situation, contrast tracks under the mucosa, similar to a dissection flap.[5] Usual discriminating symptoms from cardiac causes of chest pain are dysphagia and small-volume haematemesis. Endoscopy has been used to confirm the diagnosis, often showing a submucosal bluish mass[3,5] or organized clot,[6] occasionally with a visible mucosal tear.[1,7]

The diagnosis may be difficult and relies on exclusion of life-threatening causes, usually myocardial infarction[8] or aortic dissection.[7] Substantial morbidity may be associated with diagnostic manoeuvres. There have been case reports of haematoma mimicking malignancy, which have perforated at endoscopy,[9] or resected leading to death.[10] Negative thoracotomy has been performed to treat suspected aortic dissection,[7] only to find intramural and paraoesophageal haematoma. In the case presented here, the patient wa anticoagulated, in misguided concern for cardiac ischaemia. This aggressive anticoagulation could have precipitated or propagated the intramural haematoma.

Emergency department protocols often emphasize the early and aggressive use of anticoagulation in patients with new chest pain. This case highlights the need for careful upper GI history in these patients prior to anticoagulation. Although rare, oesophageal pathology can underlie these cases with potentially life-threatening implications as a result.

References

1. Steadman C, Kerlin P, Crimmins F *et al*. Spontaneous intramural rupture of the oesophagus. *Gut* 1990; **31**: 845–9.
2. Beumer JD, Devitt PG, Thompson SK. Intramural oesophageal dissection. *ANZ J. Surg.* 2010; **80**: 91–5.
3. Kwan KL, Law S, Wong KH, Kwok KF. Esophageal hematoma: a masquerade of rare occurrence. *Endoscopy* 2006; **38** (Suppl. 2): E29.
4. Basso L, Tocchi A. Total dysphagia from intramural haematoma following sclerotherapy for oesophageal varices. *Br. J. Surg.* 1993; **80**: 127–8.
5. Rossaak J, Wakeman C, Coulter G. Spontaneous submucosal haematoma of the oesophagus. *N. Z. Med. J.* 2006; **119**: U2342.
6. Hong M, Warum D, Karamanian A. Spontaneous intramural esophageal hematoma (IEH) secondary to anticoagulation and/or thrombolysis therapy in the setting of a pulmonary embolism: a case report. *J. Radiol. Case Rep.* 2013; **7**: 1–10.
7. Sen A, Lea RE. Spontaneous oesophageal haematoma: a review of the difficult diagnosis. *Ann. R. Coll. Surg. Engl.* 1993; **75**: 293–5.
8. Tunnicliffe G, Raymond N, Nowitz M. An unexpected diagnosis after unstable angina. *Lancet* 2007; **369**: 964.
9. Skillington PD, Matar KS, Gardner MA, Parkes RP, Cole PH. Intramural haematoma of the oesophagus complicated by perforation. *Aust. N. Z. J. Surg.* 1989; **59**: 430–2.
10. Thompson NW, Ernst CB, Fry WJ. The spectrum of emetogenic injury to the esophagus and stomach. *Am. J. Surg.* 1967; **113**: 13–26.

Ruelan V. Furtado,* MBBS
William F. Beasley,* MBBS, FRCS
Katerina Mastrocostas,† MBBS, MPH
Gregory L. Falk,* MBBS, FRACS
*Department of *Surgery and †Radiology, Concord Repatriation General Hospital, Concord, New South Wales, Australia*

doi: 10.1111/ans.12562

EARLY SYMPTOMATIC RESULTS OF LAPAROSCOPIC HELLER'S MYOTOMY AND FUNDOPLICATION FOR ACHALASIA

M.A. Richardson, R.I. Harrison, G.L. Falk

Sydney - AUSTRALIA

Achalasia is an oesophageal motility disorder characterized by a non-relaxing lower oesophageal sphincter and poor or absent motility of the oesophageal body. Treatment is symptomatic [1] *and involves disruption of the lower oesophageal sphincter, either by forceful balloon dilatation or surgical division. Although this does not address the underlying poor oesophageal motility, a substantial improvement in symptoms results in the majority of patients* [2].

The morbidity of surgical access (laparotomy or thoracotomy) in the past had lead to balloon dilatation being the favoured treatment. However, since the description in 1992 by Cuschieri and Shimi [3], *oesophageal myotomy by the minimally invasive route has been shown to effectively palliate the symptoms of achalasia with low morbidity and mortality. The potential advantage of the surgical approach is the ability to control reflux by a suitable fundoplication, an option not available to endoscopic therapy.*

This paper describes our experience in the treatment of achalasia, and the results obtained in our first 20 patients.

KEY WORDS: **Laparoscopy, Heller, Myotomy, Achalasia, Fundoplicalion.**

PATIENTS AND METHODS

Between April 1993 and May 1997, 20 patients (12 female, 8 male) underwent a laparoscopic Heller's myotomy for achalasia. The median age was 35 years (range 19 - 70 years).

All patients presented with dysphagia; three with frequent regurgitation and two patients had significant weight loss.

One or more balloon dilatations had been performed prior to surgery in seven of the 20 patients (35 %).

Diagnosis was by Barium swallow, endoscopy and oesophageal manometry (Synectics Medical, water perfused, four channel radial side hole manometry catheter).

SURGICAL TECHNIQUE

Under general anaesthesia, the patient was placed in the lithotomy position, with the operating table tilted in the head up position. Routine use of a sequential calf compression device and preoperative subcutaneous heparin were employed as prophylaxis of thromboembolic complications.

A standardised 5 port laparoscopic technique was used.

The lower oesophagus and gastric fundus were fully mobilised, and the anterior vagus nerve was identified and preserved.

A 6 - 8 cm anterior oesophageal myotomy was performed using scissor or hook diathermy, taking care not to injure the underlying mucosa.

The myotomy was extended onto the stomach by 0.5-1 cm. The completeness of the myotomy was assessed during the procedure by endoscopic assessment of the opening of the gastroesophageal junction by insufflation of air.

A 270 degrees partial posterior fundoplication was then fashioned after a hiatal repair, the wrap being sutured to the exposed muscle edges of the myotomy, and to the opposed crura.

POST-OPERATIVE CARE AND FOLLOW-UP

Oral intake was commenced on the day following surgery after a water soluble contrast swallow confirmed no leakage at the myotomy site. Patients were discharged when tolerating a free fluid diet.

Routine clinical follow-up was performed by the operating surgeon at four to six weeks postoperatively, also

DYSPHAGIA SCORE		
Food	**Meal score**	**Always, sometimes or never (x 0, 0.5 or 1)**
Water	1	
Milk	2	
Custard	3	
Jelly	4	
Scrambled egg	5	
Baked fish	6	
White bread	7	
Apple	8	
Steak	9	
Total	*Maximum 45*	
Total dysphagia = 0 No dysphagia = 45		

Table I *Patients were asked whether they had any dysphagia (always, sometimes or never) with the following nine foods. A score from 45 (no dysphagia) to 0 (total dysphagia) was then determined.*

all patients were interviewed by telephone at three months. A previously validated dysphagia (Table I) [4] score was used to assess the results of surgery, and where possible, follow-up endoscopy and oesophageal manometry were performed.

RESULTS

The procedure was completed by laparoscopy in all 20 patients. Eighteen patients underwent a Heller's myotomy and Toupet (posterior partial) fundoplication; the remaining two patients underwent a Heller's myotomy and Dor patch.

Cholecystectomy was undertaken in two of the 20 patients.

There were no specific surgery related complications reported by the patients, in particular no wound or chest infections requiring treatment.

Inadvertent mucosal perforations occurred in 2 patients at the time of their procedure, each being repaired by laparoscopy and Dor fundoplication.

SUBJECTIVE ASSESSMENT	
Result of surgery	**Number of patients**
Excellent	6
Good	12
Fair	1
Poor	1

Table II

Neither patient was shown to have an oesophageal leak on postoperative contrast studies.

There were no deaths.

The median postoperative hospital stay was 3 days (range 2-8 days).

All twenty patients were reviewed by interview at a median time of 23 months (range 5-54 months). Good or excellent results were reported in eighteen of the 20 patients when interviewed postoperatively (Table II). This subjective assessment was reflected in an improvement in dysphagia scores (Table III).

Two patients reported a less than satisfactory result:

- the first patient reported an initial significant improvement in dysphagia, with early recurrence of symptoms by 3 months post-operatively. Endoscopy and manometry demonstrated a high pressure zone at the level of the hiatus which failed to respond to dilatation. It is suspected that this is due to hiatal fibrosis. The patient has declined further intervention;

- the second patient reported continued dysphagia and left scapular pain postoperatively. Oesophageal manometry showed high pressure spasm in the oesophageal body. A thoracoscopic oesophageal myotomy performed 15 months after the original surgery resulted in improved swallowing and incomplete resolution of the scapular pain.

Eleven of the 20 patients have undergone postoperative investigation as part of follow-up or to investigate ongoing symptoms: nine patients have undergone post-operative endoscopy and the only significant findings were of a tight gastrooesophageal junction in one patient (as previously described), and evidence of oesophageal stasis in two.

Four patients had 24 hour pH monitoring and one patient recorded an elevated acid exposure of 15% (normal < 4%), which was related to a single nocturnal reflux event which failed to clear.

DISCUSSION

Achalasia is a severe oesophageal motility disorder characterized by a hypertensive lower oesophageal sphincter with atypical or no relaxation and diminished or absent motility of the oesophageal body. Disruption of the non-relaxing lower oesophageal sphincter, either by surgery or forceful pneumatic dilatation, provides good palliation for patients with achalasia. Surgery appears to provide the highest rate of relief of dysphagia [5, 6], however the morbidity related to anaesthesia and surgical access (laparotomy or thoracotomy) has resulted in dilatation being the favoured treatment in the past.

Forceful dilatation of the lower oesophageal sphincter carries the risk of perforation, reportedly ranging 2 -16% [7] with a single treatment success of 60-65% [7]. Surgical myotomy is a precise division of the lower oesophageal sphincter, and allows good visualisation and repair of any

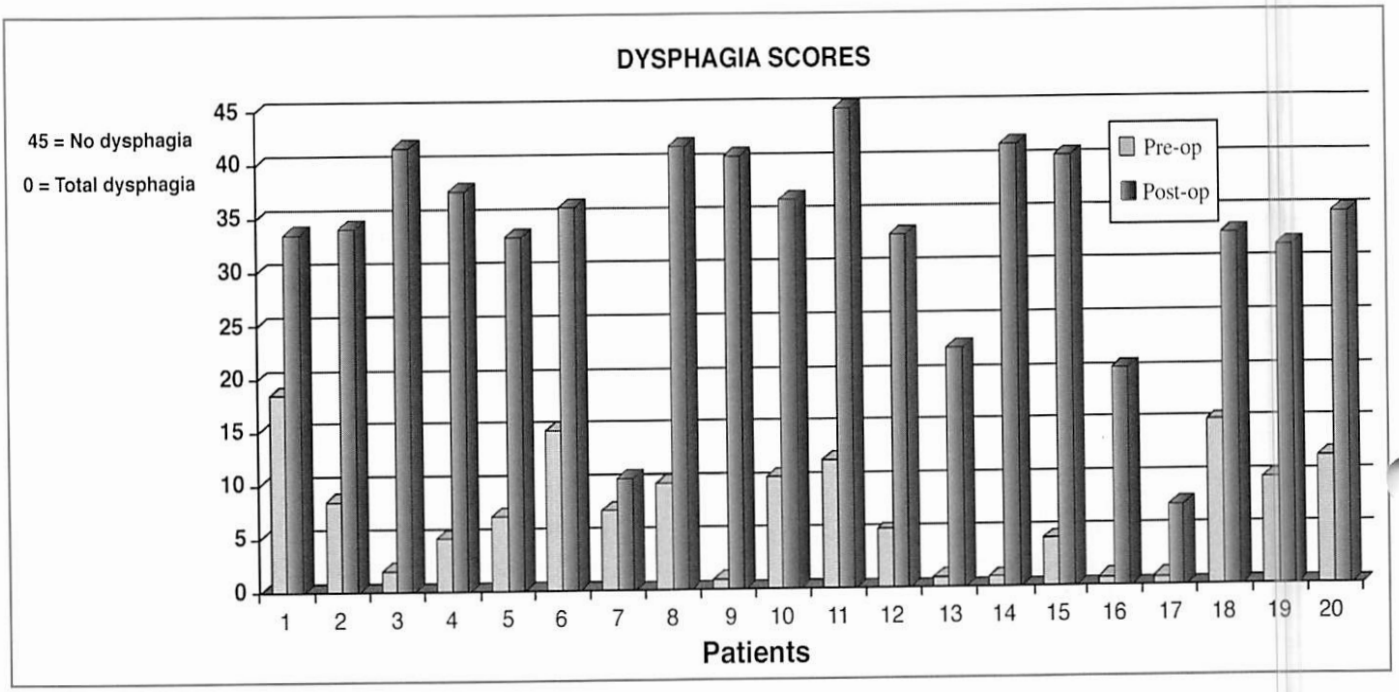


Table III

mucosal perforation. Treatment success is reported at 85-94 % [7, 9], in this series is 90 %.

Surgery also offers the opportunity to perform an antireflux procedure. The incidence of reflux following treatment for achalasia without an antireflux procedure (dilatation or surgical) ranges 10-35 % and can be diminished by the addition of an antireflux procedure.

Many patients who present for a surgical myotomy have undergone one or more balloon dilatations which have failed to palliate their symptoms. It has been suggested that previous balloon dilatation makes a myotomy more difficult and so more hazardous to perform [10]. Scarring from previous dilatation may make the establishment of a submucosal plane more difficult. This has not been our experience, and neither patient in which an inadvertent mucosal perforation occurred had undergone a previous dilatation.

The usual types of antireflux procedure described in achalasia are the Toupet partial fundoplication and the Dor patch. The Toupet fundoplication is a proven, effective antireflux measure [11], and when performed with a myotomy can be sutured to the edges of the myotomy in order to prevent recurrence of dysphagia. It has been our routine practice to perform a Toupet fundoplication in situations of poor oesophageal motility when treating gastrooesophageal reflux disease, and we have continued to do so with achalasia. The Dor patch provides a buttress for the exposed oesophageal mucosa, [12, 13] and this may be used if an operative mucosal perforation is repaired. The Dor patch was performed in 2 patients with mucosal breaches in this series. The need for an antireflux procedure is debated widely, however it is apparent that the incidence of significant gastrooesophageal reflux is higher after performing a myotomy via the abdominal approach as opposed to a thoracic approach [14]. Extending the myotomy onto the gastric wall, as is usually performed when an abdominal approach is utilised, is associated with a higher incidence of reflux [15, 16], and hence our preference to perform an antireflux procedure.

Laparoscopic Heller's myotomy with partial fundoplication can be performed with low morbidity while providing good to excellent results. The hospital stay is short and early recovery the norm. It has become the treatment of choice for achalasia in our unit.

Correspondance to
Dr. Gregory L. Falk
Head: Endosurgey
Concord Hospital
PO Box 1085 Strathfield NSW 2135
e-mail: gregfalk@sydneygisurgeons.com.au

SUMMARY

The results of the treatment of a series of patients with achalasia with a laparoscopic Heller's myotomy are reported. From April 1993 to May 1997, 20 patients underwent surgery. Patients were assessed preoperatively by Barium swallow, endoscopy and oesophageal manometry. A laparoscopic Heller' s myotomy and Toupet fundoplication were performed in 18 patients, and a laparoscopic Heller's myotomy and Dor patch in 2 patients. Symptomatic results were reported as good or excellent in 18 of the 20 patients after median follow up of 23 months (range 5 - 54 months) correlating with results gained on objective testing using a validated dysphagia score. Morbidity was minimal, and there were no deaths. Median postoperative hospital stay was 3 days (range 2- 8 days). Laparoscopic Heller's myotomy and fundoplication can be performed with low morbidity, and provide good to excellent results in the majority of patients.

RÉSUMÉ

Les auteurs rapportent les résultats (Tableau III) du traitement par myotomie laparoscopique selon Heller, d'une série de patients présentant une achalasie. D'avril 1993 à mai 1997, 20 patients ont été opérés. Ils ont été évalués avant l'intervention par un transit baryté œso-gastrique, une endoscopie et une manométrie œsophagienne. Une myotomie de Heller et une fundoplicature de Toupet par laparoscopie ont été réalisées chez 18 patients et une myotomie de Heller laparoscopique avec patch de Dor chez 2 patients. Les résulats symptomatiques sont rapportés comme bons ou excellents chez 18 des 20 patients (Tableau II) après un suivi moyen de 23 mois (extrêmes 5 -54 mois) corrélés avec les résulatst obtenus (Tableau III) par un test objectif utilisant un score de dysphagie validé (Tableau I). La morbidité a été minime, et il n'y a eu aucun décès. Le séjour hospitalier moyen a été de 3 jours (extrêmes 2-8 jours).

La myotomie de Heller par laparoscopie avec fundoplicature peut être réalisée avec un faible morbidité, et donne des résultats jugés bons à excellents chez la majorité des patients.

MOTS CLÉS : **Cœlioscopie, Heller, Myotomie, Achalasie, Fundoplicature.**

BIBLIOGRAPHY

1 - MESHKINPOUR H., HAGHIGHAT P., MESHKINPOUR A.: Quality of life among patients treated for achalasia: *Dig. Dis. Sci, 1996, 41 (2), 352-356.*

2 - MAKELA J., KIVINIEMI H., LAITINEN S.: Heller's cardiomyotomy compared with pneumatic dilatation for treatment of oesophageal achalasia: *Eur. J. Surg., 1991, 157, 411-414.*

3 - SHIMI S., NATHANSON L.K., CUSCHIERI A.: Laparoscopic cardiomyotomy for achalasia: *J. R. Coll. Surg. Edinb., 1991, 36, 152.*

4 - DAKKAK M., BENNETT J.R.: A new dysphagia score with objective validation: *J. Clin. Gastroenterol., 1992, 14 (2), 99- 100.*

5 - ANSELMINO M., PERDIKIS G., HINDER R.A., POLISHUK P.V., WILSON P., TERRY J.D., LANSPA S.J.: Heller myotomy is superior to dilatation for the treatment of early achalasia: *Arch. Surg., 1997, 132 (3), 233-240.*

6 - SWANSTROM L.L., PENNINGS J.: Laparoscopic esophagomyotomy for achalasia: *Surg. Endosc., 1995, 9 (3), 286-290.*

7 - MITCHELL P.C., WATSON D.I., DEVITT P.G., BRITTEN-JONES R., MAC DONALD S., MYERS J.C., JAMIESON G.G.: Laparoscopic cardiomyotomy with a Dor patch for achalasia: *Can. J. Surg., 1995, 38 (5), 445-448.*

8 - ODDSDOTTIR M.: Laparoscopic management of achalasia: *Surg. Clin. North. Am., 1996, 76 (3), 451-458.*

9 - PARRILLA PARICIO P., MARTINEZ DE HARO L., ORTIZ A., AGUAYO J.L.: Achalasia of the cardia: long-term results of oesophagomyotomy and posterior partial fundoplication: *Br. J. Surg., 1990, 77 (12), 1371-1374.*

10 - JORGENSEN J.O., HUNT D.R.: Laparoscopic management of pneumatic dilatation resistant achalasia.: *Aust. N. Z. J. Surg., 1993, 63 (5), 386-388.*

11 - CROOKES P.F., WILKINSON A.J., JOHNSTON G.W.: Heller's myotomy with partial fundoplication: *Br. J. Surg., 1989, 76 (1), 99-100.*

12 - ANCONA E., ANSELMINO M., ZANINOTTO G., COSTANTINI M., ROSSI M., BONAVINA L., BOCCU C., BUIN F., PERACCHIA A.: Esophageal achalasia: laparoscopic versus conventional open Heller-Dor operation: *Am. J. Surg., 1995, 170 (3), 265-270.*

13 - ANCONA E., PERACCHIA A., ZANINOTTO G, ROSSI M., BONAVINA L., SEGALIN A.: Heller laparoscopic cardiomyotomy with antireflux anterior fundoplication (Dor) in the treatment of esophageal achalasia: *Surg. Endosc., 1993, 7 (5), 459-461.*

14 - ANDREOLLO N.A., EARLAM R.J.: Heller's myotomy for achalasia: is an added anti-reflux procedure necessary: *Br. J. Surg., 1987, 74 (9), 765-769.*

15 - ELLIS F.H.: Oesophagomyotomy for achalasia: a 22-year experience: *Br. J. Surg.: 1993, 80, 882-885.*

16 - HUNTER J.G., TRUS T.L., BRANUM G.D., WARING J.P.: Laparoscopic Heller myotomy and fundoplication for achalasia: *Ann. Surg. 1997, 225 (6), 655-664.*

REVISION HIATAL SURGERY

Failing anti reflux surgery is recognised as a difficult problem of treatment and reoperation, the second and third procedures delivering diminished functional outcome often caused by abnormal physiology generated by previous surgery or primary unrecognised abnormality at initial surgery. The importance of physiological initial investigation is highlighted. Multiple different diagnostic and technical problems can arise in the situation of recurrent hiatus hernia or recurrent reflux symptomatology. Repeat operations are renowned for becoming increasingly problematic for the patient with high levels of morbidity. Symptoms are frequently not related to reflux disease itself and careful physiological diagnosis has become necessary to achieve adequate results. Care of these patients became an ongoing pursuit in my practice to establish abnormal physiology and tailor revisional surgery to the symptoms and abnormalities identified. The service I established received patients for diagnosis and therapy from across the state. This resulted in an extensive experience equivalent to world-class centres. The continued patients accessing the revision service is allowing continued physiological investigation and development of surgical techniques, depending on types of abnormality causing symptomatic or anatomical failure.

References:

1. Robertson JP, Van der Wall H, Falk GL. Failed fundoplication with delayed gastric emptying: efficacy of subtotal gastrectomy. ANZ Journal of Surgery. 2022;n/a(n/a).

2. Suppiah A, Sirimanna P, Vivian SJ, O'Donnell H, Lee G, Falk GL. Temporal patterns of hiatus hernia recurrence and hiatal failure: quality of life and recurrence after revision surgery. Dis Esophagus. 2017;30(4):1-8.

3. Furtado RV, Falk GL, Vivian SJ. Recurrence after composite repair of a giant hiatus hernia: 'the golf club' deformity is a distinctive clinical and radiological picture. Ann R Coll Surg Engl.

4. Lim JK, Moisidis E, Munro WS, Falk GL. Re-operation for failed anti-reflux surgery. Aust N Z J Surg. 1996;66(11):731-3.

ORIGINAL ARTICLE

Royal Australasian College of Surgeons

Failed fundoplication with delayed gastric emptying: efficacy of subtotal gastrectomy

Jason P Robertson ,* Hans Van der Wall† and Gregory L Falk‡

*Department of Surgery, North Shore Hospital, Auckland, New Zealand
†School of Medicine, University of Notre Dame, Australia CNI Meadow bank, Sydney, New South Wales, Australia and
‡Department of Upper Gastro-Intestinal Surgery, Concord Repatriation General Hospital, Sydney, Australia

Key words
gastrectomy, reflux, Roux en Y.

Correspondence
Mr. Jason Robertson, Upper Gastrointestinal Surgery Unit, North Shore Hospital, 124 Shakespeare Road, Takapuna, Auckland, New Zealand.
Email: jrobertson171@gmail.com

Jason P Robertson MBChB, MMedSc, FRACS; **H. Van der Wall** MBBS, PhD, D MedSc, FRACP; **Gregory L Falk** MBBS, FRACS, FACS.

Accepted for publication 19 December 2021.

doi: 10.1111/ans.17460

Abstract

Background: The management of patients with gastroparesis and recurrent reflux after previous fundoplication is challenging. The aim of this study was to evaluate the safety and efficacy of subtotal gastrectomy with Roux-en-Y reconstruction as a remedial procedure in this select patient population.

Method: Retrospective analysis of a prospectively populated database identified all patients that underwent subtotal gastrectomy with Roux-en-Y reconstruction (SGRNY) due to reflux symptoms and delayed gastric emptying (DGE). Demographic, intra-operative and post-operative data including pre and post-operative modified reflux aspiration scintigraphy studies were evaluated. Standardized questionnaires were used to assess symptomatic outcomes.

Results: From 2018 SGRNY has been selectively performed in 13 patients. Preoperative workup confirmed DGE and severe symptomatic reflux in all patients. The median number of previous fundoplication and or hiatal hernia operations was two (range 1–3). The mean hospital length of stay was 10 ± 6 days. Post-operative morbidity was experienced in three patients (23%). Seven patients (64%) had significant improvement or complete resolution of reflux on post-operative scintigraphy. Symptom improvement was reported in 92% of patients.

Conclusion: In a select patient cohort with post-fundoplication reflux and DGE symptoms, SGRNY is a moderately safe and effective salvage option.

Introduction

In patients with refractory gastro-oesophageal reflux disease (GORD), antireflux surgery provides symptom resolution in 85–90% of patients at 5 year follow-up.[1] However, 3–7% of patients develop recurrent symptoms that necessitate reoperative surgery.[2] Remedial antireflux surgery is challenging and successful outcomes are dependent upon many factors. With each revisional operation the incidence of a poor symptomatic outcome rises significantly.[2–4]

Vagal nerve malfunction following previous surgery can cause refractory symptomatic delayed gastric emptying (DGE).[5,6] In selected, highly symptomatic patients, after exhausting medical interventions, a salvage subtotal gastrectomy with Roux-en-Y reconstruction (SGRNY) has been reported to be an effective approach to managing symptoms of recurrent reflux and DGE, however high post-operative morbidity rates of 40–67% have precluded its widespread utilization.[6–8] In 2018 we adopted SGRNY as a salvage procedure in this patient population due to post recurrent fundoplication experience. There remains a paucity of studies specifically evaluating this patient population and the peri-operative risks, symptomatic outcomes and patient satisfaction.

Methods

Data collection

All patients who underwent SGRNY after one or more failed anti-reflux procedures were identified from a prospectively maintained database. Patients undergoing gastrectomy for reasons other than recurrent reflux symptoms with DGE were excluded from analysis. Relevant demographic, operative, and postoperative data on the initial and revision surgical procedures were collected retrospectively for all patients. Thirty day post-operative readmission and complications were recorded, and graded according to the Clavien–Dindo (CD) classification.[9] Institutional ethics 219/eth07856 approval was obtained.

Patient evaluation

Preoperative workup included upper endoscopy, oesophageal manometry and modified scintigraphic assessment of reflux events and liquid gastric emptying.

Oesophageal manometry was performed using a standard technique with a water-perfused dent sleeve eight-channel catheter (Dent Sleeve International, Mississauga, Ontario, Canada). Oesophageal motility disorders were grouped by a modified grade similar to that described by Kahrilas *et al*.[10] Patients with 2–3/10 ineffective swallows were labelled as having 'mild', 4–5 as 'moderate' and 6 or more ineffective swallows as 'severe' oesophageal dysmotility. Mild motility disorder in this grading was considered normal.

Modified reflux aspiration scintigraphy was conducted using an extensively validated technique.[11] Scintigraphy was performed after an overnight fast using Hawkeye 4 gamma camera (General Electric, Milwaukee, USA) with stomach, chest, and upper airway in the field of view. A 40–60 MBq of 99mTc DTPA was administered orally mixed with 150–200 mL of water. Aspiration was demonstrated on delayed images at 2 h by the presence of isotope in the lungs.

Biliary reflux was investigated using intravenous injection of 99mTc Hepatolite. Biliary reflux/aspiration was confirmed by tracer contamination of the pharynx, laryngopharanx or airways on SPECT/CT images.[12]

Liquid DGE was evaluated on scintigraphy as part of the reflux aspiration study. A time to half clearance of the liquid tracer of >16 minutes was considered prolonged.[13] The diagnosis of DGE was supported by clinical symptoms of bloating, nausea and/or vomiting of food ingested >3 h prior.[14] Evidence of solid food in the stomach on endoscopy after a > 6 h fast was considered diagnostic of DGE.[15] Further confirmation of DGE with 99 m Tc labelled standardized solid meal gastric emptying study was performed when indicated. All patients had a strong clinical diagnosis of DGE based upon symptoms and delayed clearance of liquid tracer on scintigraphy. Further objective evidence of DGE on solid meal gastric emptying study or endoscopy was required prior to proceeding to surgery. Barium swallow, computed tomography (CT) scan and 24-h pH monitoring were performed as clinically indicated.

Table 1 Patient characteristics and preoperative assessment ($n = 13$)

Variable	*N*
Female	11 (85%)
Age (years) (mean ± SD)	64 ± 10.6
BMI (kg/m^2) (mean ± SD)	30.3 ± 7.6
ASA 1	0 (0%)
ASA 2	6 (46%)
ASA 3	7 (54%)
Previous pyloroplasty	5 (38%)
360° Fundoplication at time of SGRNY	10 (77%)
IOm on Manometry	7 (54%)
Severe IOM	6 (46%
Moderate IOM	1 (8%)

Abbreviations: IOM, ineffective oesophageal motility; SD, standard deviation; SGRNY, salvage subtotal gastrectomy with Roux-en-Y reconstruction.

In the presence of severe symptomatology, following the comprehensive work-up, failure of maximal medical treatment and preoperative counselling patients were considered for SGRNY.

Surgical technique

Management was under the care of a single surgeon. Midline laparotomy was utilized in all patients. Subtotal gastrectomy and selective hiatal dissection were determined by pathology and symptoms. The extent of surgery possible was limited by previous scarring and adhesions. Stapled or hand sewn Roux-en-Y gastrojejunostomy was performed (Echelon stapling device: Ethicon: Johnson & Johnson company). The afferent limb was planned to be 50 cm, and the efferent limb 60–70 cm long and preferentially placed retro-colic (unless contraindicated by adhesions.) Cruroplasty was performed with 0 Ethibond sutures (Ethicon: Johnson & Johnson company). A jejuno-jejunostomy was completed with the 60-mm linear stapler and closure of the common enterotomy with continuous 3–0 PDS suture (Ethicon: Johnson & Johnson company) with closure of mesenteric defects.

Patient assessment of outcomes

Patients were reviewed clinically and received a standardized questionnaire post-operatively at six monthly intervals. Questionnaires were self-administered, assessed satisfaction with the operation, improvement in symptoms, and whether the patient would recommend the operation to family and friends. Medication for reflux symptoms were recorded. When multiple questionnaires were completed, the most recent questionnaire outcomes were analysed.

Results

Review of all patients in the antireflux surgery database ($n = 3157$) identified 13 patients that underwent SGRNY due to reflux and DGE between November 2018 and October 2020. Patient characteristics are listed in Table 1. The median number of previous fundoplications/hiatal operations was two (range 1–3). Prior 360° fundoplication and pyloroplasty were performed in 77% ($n = 10$) and 38% ($n = 5$) of patients, respectively. SGRNY was performed a median of 3 years (range 2–12 years) after the previous surgical procedure.

Table 2 Intraoperative and post-operative outcomes

Variable	*N*
Operative time (minutes) (mean ± SD)	237 ± 40
Length of stay (day) (mean ± SD)	10 ± 6
Morbidity (CD grade)	
1	1 (8%)
2	0 (0%)
3	2 (15%)
4	0 (0%)
All morbidity	3 (23%)
Post-operative nutritional supplementation	1 (8%)
30-day readmission	1 (8%)
90-day mortality	0 (0%)

Abbreviations: CD, Clavien–Dindo classification[10]; SD, standard deviation.

Table 3 Post-operative subjective and objective outcome measures

Patient	How satisfied are you with the results of your operation? 1. Not satisfied 2. Satisfied 3. Very satisfied	Following surgery, are you: 0. Worse 1. Same 2. Improved partially 3. Fully improved	Would you recommend this operation to friends or family?	Aspiration present on Preoperative Modified reflu× aspiration scintigraphy	Aspiration present on postoperative Modified reflu× aspiration scintigraphy	Ongoing acid suppression medication required
1	2	2	Yes	Yes	Yes	No
2	3	3	Yes	Yes	No	No
3	3	2	Yes	No	No	No
4	1	0	No	Biliary aspiration	Biliary aspiration	Yes
5	1	2	Yes	Yes	Yes	No
6	2	2	No	No	Biliary aspiration	Yes
7	–	–	–	Yes	–	–
8	3	3	Yes	Yes	No	No
9	3	3	Yes	Yes	No	No
10	2	2	Yes	Yes	No	Yes
11	2	2	Yes	Yes	No	No
12	2	2	No	Yes	Trace aspiration	Yes
13	1	2	Yes	No	–	No

DGE and significant reflux were identified preoperatively in all patients on liquid aspiration scintigraphy. Correlation with symptoms and endoscopic findings confirmed the diagnosis of DGE in five patients (38%), while eight patients (62%) had DGE confirmed on a standardized solid meal gastric emptying study. Pre-operative manometry confirmed ineffective oesophageal motility (IOM) in seven (54%) patients. Reflux scintigraphy demonstrated aspiration in 10 (77%) patients, all of whom were symptomatic of aspiration events.

Intraoperative and postoperative results are displayed in Table 2. The mean operative time was 235 ± 40 min. Enterotomy occurred in four patients (31%) all were repaired intraoperatively, without post-operative morbidity. Hiatus hernia was present in four, disrupted fundoplication in four and hiatus dissection was required in seven to treat symptoms adequately. A partial fundoplication of the gastric pouch was performed in four patients. The Roux limb was placed in the retro-colic position in 10 patients (77%).

The mean hospital length of stay was 10 ± 6 days with morbidity experienced in 23% ($n = 3$). There was one wound infection (CD grade I) and two sub-diaphragmatic collections requiring percutaneous drainage (CD grade IIIa). One patient self-discharged against medical advice due to social circumstances, and required readmission for drainage within 30-days of surgery. One patient had a long-standing feeding gastrostomy preoperatively due to global gastrointestinal dysmotility. This was replaced with a feeding jejunostomy during SGRNY and continued to be necessary. No patients required new supplementary enteral or parenteral feeding post-operatively.

Post-operative digital reflux scintigraphy was available in 11 of 13 patients. Seven patients (64%) had significant improvement or complete resolution of reflux events on post-operative scintigraphy. There was no improvement in two patients, new bile reflux occurred in one, and one patient had ongoing bile reflux. Pre- and postoperative reflux aspiration scintigraphy results are presented in Table 3. Seven patients (64%) had significant improvement or resolution of aspiration of follow up testing. One patient with no aspiration on preoperative testing developed new biliary aspiration post-operatively.

Combined aspiration and IOM were present in five patients preoperatively, three patients (60%) had resolution of aspiration (all of whom had severe IOM), one patient had ongoing aspiration and one patient with moderate IOM had ongoing biliary aspiration.

Post-operative patient satisfaction data were available in 12 patients (Table 3.) One patient declined further collaboration. Median time to follow-up was 12 months (range 6–24 months). When asked 'would you recommend this operation to friends or family?' 75% of patients responded 'Yes'. Of those that responded 'No' two were satisfied with their outcome. Partial or full symptom improvement was reported in 11 patients (92%). Nine patients (75%) were either satisfied or very satisfied with their operation. Acid suppression medication was discontinued in eight patients (67%), two patients (17%) required occasional or reduced dose and two (17%) remained on the same pre-operative medication without amelioration of symptoms. In patients with concurrent oesophageal dysmotility, five patients (72%) reported satisfaction with their operation and stated they would recommend the operation to friends and family.

Discussion

The most common surgical approach to address recurrent symptoms after antireflux surgery is revision fundoplication with or without hiatal hernia repair.[2,16] However in patients requiring additional revisional surgery, repeated fundoplication has been a relatively hazardous pursuit with high recurrence rates, morbidity and occasional mortality.[16,17] A concurrent motility disorder confounds fundoplication effectiveness.[2] Motility disorders may present as DGE, oesophageal dysmotility or both. The incidence of DGE and/or oesophageal dysmotility are likely to increase with each additional episode of surgery due to fibrosis, obstructed anatomy, and damage to vagal nerves. Motility disorders are well recognized risk factors for higher morbidity and inferior symptomatic outcomes after revision surgery and are considered relative contraindications for repeated fundoplication.[2,18,19]

Patients with a concurrent diagnosis of DGE after failed fundoplication represent a very select cohort and evidence regarding management is scarce. Williams *et al*. compared SGRNY to revision fundoplication as remedial antireflux procedures for patients with a failed fundoplication and found significantly higher primary symptom resolution after SGRNY than revision fundoplication. Williams *et al*. concluded that redo fundoplication is ill advised in the setting of severe gastroparesis, however, only one patient in their study was noted to have DGE preoperatively.[7]

Two studies have specifically evaluated patients with DGE and failed fundoplication. The 2011 study by Clark *et al*. assessed the role of gastric resection in nine patients with post fundoplication DGE. Following revisional gastrectomy two patients (22%) had symptom resolution whilst seven patients (78%) had persistent symptoms. The nature of these symptoms and patient satisfaction were not specified. Post-operative morbidity occurred in three patients (33%) with a median length of stay of 10 days (7–32 days). Concerningly 33% of patients in the study required ongoing enteral nutrition at a median follow-up of 23 months.[6]

The 2013 study by Gerritson *et al*. also evaluated the role of gastrectomy in 11 patients with DGE after antireflux surgery. They reported low morbidity of 9% ($n = 1$) and a mean hospital length of stay of 12 ± 5 days. Patient satisfaction outcomes were available in nine patients, three patients (89%) reported their operation to be worthwhile, and if given the choice, five patients (55%) would undergo the same procedure again.[20]

These reports present contrasting morbidity and success rates and have significant intra- and inter-study variability in operative technique of the revisional gastrectomy; with total, subtotal, proximal and distal gastrectomies all included in the analyses.

The current study had a standardized work-up and operative approach to DGE and reflux after failed fundoplication with all included patients undergoing a SGRNY. Morbidity and LOS in our patient cohort compares favourably to the above studies. Patient assessments demonstrated encouraging symptom improvement, patient satisfaction and willingness to recommend the procedure in most cases. Objective evaluation with post-operative digital reflux scintigraphy showed a congruence of physiological improvement, reduction in aspiration and reported satisfaction outcomes.

Pulmonary aspiration of gastric refluxate is often difficult to manage. The Society of American Gastrointestinal and Endoscopic Surgeons lists pulmonary aspiration as one of the indications for anti-reflux surgery, however, there is limited objective evidence supporting fundoplication in this setting.[21] Khoma *et al*. reported 39 patients that underwent laparoscopic 360° fundoplication for confirmed aspiration of gastric refluxate on scintigraphy. On post-operative scintigraphy aspiration scans pulmonary aspiration was prevented in 61.5% of patients, however in patients with severe IOM prevention decreased to 35.7%.[22]

The current report showed a significant improvement of pulmonary aspiration in patients with severe IOM. It is likely that some patients with severe oesophageal dysmotility may lack sufficient oesophageal peristalsis to adequately clear the oesophagus especially following fundoplication, resulting in stasis or reflux of residual oesophageal fluid. Therefore, SGRNY may be an appropriate low pressure alternative with the added benefit of acid and bile diversion.

Bile reflux and aspiration after SGRNY occurred in two patients. Although both patients had Roux limbs 70 cm in length, bile reflux was still present. Bile reflux has been reported even with alimentary Roux limb lengths of up to 100 cm.[23] Lengthening the Roux limb to 100 cm has been reported to resolve symptoms.[23,24]

When managing patients with GORD and associated DGE, controversy still exist as to whether the gastric remnant should be resected or remain *in-situ*. Proponents of leaving the stomach *in-situ* cite the advantages of shorter operative time, lower risk post-operative morbidity, and the availability of a gastric conduit that can be used for oesophagectomy or reversal if required. Conversely, those in favour of resection state the potential risks of haemorrhage from the gastric remnant, the occurrence of gastro-gastric fistula, the development of marginal ulceration due to a retained antrum effect, bacterial overgrowth in the remnant, or development of a subsequent gastric carcinoma, which is not amenable to surveillance.[7,8] Furthermore, many patients may have also had a previous pyloric intervention (as was the case in 38% of patients in our study.) This can predispose the gastric remnant to bile reflux which is known to be toxic to gastric mucosa and can contribute to bile reflux gastropathy and chronic abdominal pain.[25]

The 2019 study by Landreneau *et al*. evaluated Roux en Y with stomach *in situ* (RYSIS) in comparison with Roux en Y gastrectomy (RYG) in patients with medically refractive gastroparesis. Symptomatic outcomes were equivalent following both procedures, however, patients undergoing RYSIS were more likely to require subsequent surgical intervention or remnant resection to address nausea, vomiting and abdominal pain.[8]

This study was limited by its retrospective cohort design, small sample size and short follow-up period. Additional long term follow-up of this cohort would be useful to assess the durability of successful patient outcomes.

Conclusion

In patients with post-fundoplication reflux and DGE symptoms, subtotal gastrectomy with RY reconstruction is a moderately safe and effective salvage option in this select patient population. Subtotal gastrectomy with RY reconstruction may offer additional benefits in addressing aspiration particularly in the context of severe IOM and DGE. A longer alimentary jejunal limb of the Roux-en-Y may be beneficial in outcome as suggested elsewhere.

Conflict of interest

None declared.

Author Contributions

Jason P Robertson: Conceptualization; data curation; formal analysis; investigation; methodology; validation; visualization; writing – original draft; writing – review and editing. **Hans Van der Wall:** Data curation; investigation; supervision; validation. **Gregory L Falk:** Conceptualization; data curation; methodology; supervision; writing – review and editing.

References

1. Fuchs K, Breithaupt W, Fein M, Maroske J, Hammer I. Laparoscopic Nissen repair: indications, techniques and long-term benefits. *Langenbecks Arch. Surg.* 2005; **390**: 197–202.
2. Munie S, Nasser H, Gould JC. Salvage options for fundoplication failure. *Curr. Gastroenterol. Rep.* 2019; **21**: 1–8.
3. Gronnier C, Degrandi O, Collet D. Management of failure after surgery for gastro-esophageal reflux disease. *J. Visc. Surg.* 2018; **155**: 127–39.
4. Coakley KM, Groene SA, Colavita PD *et al*. Roux-en-Y gastric bypass following failed fundoplication. *Surg. Endosc.* 2018; **32**: 3517–24.
5. Weber CE, Kanani Z, Schumm M, Helm M, Gould JC. Roux-en-Y gastric bypass as a salvage procedure in complicated patients with failed fundoplication (s). *Surg. Endosc.* 2019; **33**: 738–44.
6. Clark CJ, Sarr MG, Arora AS, Nichols FC, Reid-Lombardo KM. Does gastric resection have a role in the management of severe post-fundoplication gastric dysfunction? *World J. Surg.* 2011; **35**: 2045–50.
7. Williams VA, Watson TJ, Gellersen O *et al.* Gastrectomy as a remedial operation for failed fundoplication. *J. Gastrointest. Surg.* 2007; **11**: 29–35.
8. Landreneau JP, Strong AT, El-Hayek K, Kroh MD, Rodriguez JH. Gastrectomy versus stomach left in situ with Roux-en-Y reconstruction for the treatment of gastroparesis. *Surg. Endosc.* 2019; **1-9**: 1847–55.
9. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann. Surg.* 2004; **240**: 205–13.
10. Kahrilas PJ, Bredenoord AJ, Fox M *et al*. The Chicago classification of esophageal motility disorders, v3. 0. *Neurogastroenterol. Motility* 2015; **27**: 160–74.
11. Burton L, Falk GL, Parsons S, Cusi M, Van Der Wall H. Benchmarking of a simple scintigraphic test for gastro-oesophageal reflux disease that assesses oesophageal disease and its pulmonary complications. *Mol. Imaging Radionucl. Ther.* 2018; **27**: 113–20.
12. Falk GL, Gooley SC, Burton L, Van der Wall H. Novel biliary reflux-aspiration scanning identifies a cause of refractory symptoms and pulmonary aspiration in complex reflux disease. *Mol. Imag. Radionuclide Ther.* 2021.
13. Podolsky DK, Fitz JG, Kalloo AN, Shanahan F, Wang TC. *Gastric Motility and Gastric Emptying*. Hoboken, New Jersey, USA: John Wiley & Sons Ltd., 2015.
14. Pathikonda M, Sachdeva P, Malhotra N, Fisher RS, Maurer AH, Parkman HP. Gastric emptying scintigraphy: is four hours necessary? *J. Clin. Gastroenterol.* 2012; **46**: 209–15.
15. Coleski R, Baker JR, Hasler WL. Endoscopic gastric food retention in relation to scintigraphic gastric emptying delays and clinical factors. *Dig. Dis. Sci.* 2016; **61**: 2593–601.
16. Del Campo SEM, Mansfield SA, Suzo AJ, Hazey JW, Perry KA. Laparoscopic redo fundoplication improves disease-specific and global quality of life following failed laparoscopic or open fundoplication. *Surg. Endosc.* 2017; **31**: 4649–55.
17. Devitt PG, Iyer PV, Rowland R. In: Jamieson G (ed). *Surgery of the Oesophagus*. London, England: Churchill Livingstone, 1988.
18. Landreneau JP, Strong AT, Kroh MD, Rodriguez JH, El-Hayek K. Minimally invasive Roux-en-Y reconstruction as a salvage operation after failed nissen fundoplication. *Surg. Endosc.* 2020; **34**: 2211–8.
19. Giulini L, Razia D, Mittal SK. Redo fundoplication and early Roux-en-Y diversion for failed fundoplication: a 3-year single-center experience. *Surg. Endosc.* 2021; 1–6. https://doi.org/10.1007/s00464-021-08610-y
20. Gerritsen A, Furnée EJ, Gooszen HG, Wondergem M, Hazebroek EJ. Evaluation of gastrectomy in patients with delayed gastric emptying after antireflux surgery or large hiatal hernia repair. *World J. Surg.* 2013; **37**: 1065–71.
21. Jobe BA, Richter JE, Hoppo T *et al*. Preoperative diagnostic workup before antireflux surgery: an evidence and experience-based consensus of the esophageal diagnostic advisory panel. *J. Am. Coll. Surg.* 2013; **217**: 586–97.
22. Khoma O, Falk SE, Burton L, Van der Wall H, Falk GL. Gastro-oesophageal reflux and aspiration: does laparoscopic fundoplication significantly decrease pulmonary aspiration? *Lung* 2018; **196**: 491–6.
23. Swartz DE, Mobley E, Felix EL. Bile reflux after Roux-en-Y gastric bypass: an unrecognized cause of postoperative pain. *Surg. Obes. Relat. Dis.* 2009; **5**: 27–30.
24. Collard J-M, Romagnoli R. Roux-en-Y jejunal loop and bile reflux. *Am. J. Surg.* 2000; **179**: 298–303.
25. Kumar N, Thompson CC. Remnant gastropathy due to bile reflux after Roux-en-Y gastric bypass: a unique cause of abdominal pain and successful treatment with ursodiol. *Surg. Endosc.* 2017; **31**: 5399–402.

Diseases of the Esophagus (2017) **30**, 1–8
DOI: 10.1093/dote/dow035

DISEASES OF THE ESOPHAGUS

ISDE The International Society for Diseases of the Esophagus

Original Article

Temporal patterns of hiatus hernia recurrence and hiatal failure: quality of life and recurrence after revision surgery

A. Suppiah,[1] P. Sirimanna,[1,2] S. J. Vivian,[3] H. O'Donnell,[3] G. Lee,[3] G. L. Falk[1,2,3]

[1] *Concord Repatriation General Hospital, Sydney, Australia,* [2] *The University of Sydney, NSW2006, Australia, and* [3] *Sydney Heartburn Clinic, Lindfield, Australia, 2070*

SUMMARY. **Antireflux and paraesophageal hernia repair surgery is increasingly performed and there is an increased requirement for revision hiatus hernia surgery. There are no reports on the changes in types of failures and/or the variations in location of crural defects over time following primary surgery and limited reports on the outcomes of revision surgery. The aim of this study is to report the changes in types of hernia recurrence and location of crural defects following primary surgery, to test our hypothesis of the temporal events leading to hiatal recurrence and aid prevention. Quality of life scores following revision surgery are also reported, in one of the largest and longest follow-up series in revision hiatus surgery. Review of a single-surgeon database of all revision hiatal surgery between 1992 and 2015. The type of recurrence and the location of crural defect were noted intraoperatively. Recurrence was diagnosed on gastroscopy and/or contrast study. Quality of life outcomes were measured using Visick, dysphagia, atypical reflux symptoms, satisfaction scores, and Gastrointestinal Quality of Life Index (GIQLI). Two-hundred eighty four patients (126 male, 158 female), median age 60.8(48.2–69.1), underwent revision hiatal surgery. Median follow-up following primary surgery was 122.8(75.3–180.3) and 91.6(40.5–152.5) months after revision surgery. The most common type of hernia recurrence in the early period after primary surgery was 'telescope'(42.9%), but overall, fundoplication apparatus transhiatal migration was consistently the predominant type of recurrence at 1–3 years (54.3%), 3–5 years (42.5%), 5–10 years (45.1%), and >10 years (44.1%). The location of crural defects changed over duration following primary surgery as anteroposterior defects was most common in the early period (45.5% in <1 year) but decreased over time (30.3% at 1–3 years) while anterior defects increased in the long term with 35.9%, 40%, and 42.2% at 3–5 years, 5–10 years, and >10 years, respectively. Revision surgery intraoperative morbidity was 19.7%, mainly gastric (9.5%) and esophageal (2.1%) perforation. There was a 75% follow-up rate and recurrence following revision surgery was 15.4%(44/284) in unscreened population and 21%(44/212) in screened population. There was no difference in recurrence rate based on size of hiatus hernia at primary surgery, or at revision surgery. There were significant improvements in the Visick score (3.3 vs. 2.4), the modified Dakkak score (23.2 vs. 15.4), the atypical reflux symptom score (23.7 vs. 15.4), and satisfaction scores (0.9 vs. 2.2), but no difference in the various domains (symptom, physical, social, and medical) of the GIQLI scores following revision surgery. Revision hiatal surgery has higher intraoperative morbidity but may achieve adequate long-term satisfaction and quality of life. The most common type of early recurrence following primary surgery is telescoping, and overall is wrap herniation. Anterior crural defects may be strong contributor to late hiatus hernia recurrence. Symptom-specific components of GIQLI, but not the overall GIQLI score, may be required to detect improvements in QOL.**

KEY WORDS: **antireflux surgery, hiatal hernia, large hiatal hernia, quality of life.**

INTRODUCTION

Hiatal hernia repair and antireflux surgery have excellent long-term outcome but has been reported with large variations in hiatal hernia recurrence of 5%–42%.[1,2] A recent meta-analysis of 13 studies in 965 patients reported mean 14% hernia recurrence in unscreened postsurgical patients, which increased to 25% recurrence in routinely screened patients.[1] This was supported by a systematic review, which also reported 25% hiatus hernia recurrence in patients undergoing routine screening with contrast swallow.[2] The appreciation of the excellent outcomes of primary antireflux surgery[3,4] and the introduction of minimal

Address correspondence to: Assoc Prof Gregory L. Falk, University of Sydney, Department Head Upper Gastrointestinal Surgery- RGH Concord Sydney, Sydney Heartburn Clinic, The Lindfield Centre, 12 Tryon Road, Sydney, NSW 2070, Australia. Email: sydney.heartburn@gmail.com
Conflicts of interest: The authors declare that they have no conflict of interest.

invasive approaches have led to increased number of primary antireflux procedures with subsequent increased numbers of hiatal recurrences and demand for revision hiatal surgery.[5,6] However, there are only a few reports on outcomes of revision hiatal surgery, which have mostly associated revision surgery with higher morbidity, and potentially decreased symptomatic success compared to primary surgery.[7–11] Furthermore, the temporal changes in types of hiatus hernia recurrence and the part of the diaphragm repair that fail after primary surgery have never been investigated. We aimed to report the observed changes in types of hiatal hernia recurrence, and the location of crural failure following primary surgery and to test our hypothesis of temporal events leading to hiatal recurrence (see Methods: Classifications of Failure). We also aimed to report the outcome of revision surgery as defined by further hernia recurrence and quality of life scores.

MATERIALS AND METHODS

Data were collected from a prospectively maintained single-surgeon database of revisional hiatal surgery from 1992 to 2015. All patients underwent endoscopy, contrast radiography, and 24-hour pH and manometry. Standardized novel reflux-aspirate technetium scans were used for patient with atypical or upper respiratory symptoms.[12]

Selection criteria

Revision surgery was only considered when there was a clinical correlation between a recurrent and typical symptom (e.g. heartburn) with objective evidence of recurrence/reflux in at least one of the investigations. Patients reporting a new unexplained symptom after primary surgery were not offered surgery unless it was dysphagia with confirmed manometric evidence of an isolated high-pressure zone in the surgical field. For patients with atypical symptoms (e.g. cough), laryngopharyngeal reflux must be demonstrated on technetium scan regardless of evidence of hernia recurrence/reflux on other investigations. All surgical patients had also failed trial of medical management. Patients with symptoms only (regardless of how convincing) but without objective evidence on any investigations were not offered surgery.

Ethics approval was by RGH Concord Institutional Ethics approval for maintenance reporting (Database, serially approved CH62/6/2011-092). Hiatus hernia at primary surgery was classified as none, small (1–5 cm), and large (>5 cm). Hiatus hernia noted at time of revision surgery was classified as none, small (0–2 cm), moderate (2–5 cm and/or <30% intrathoracic migration), large (>5–10 cm defect and/or 30%–50% intrathoracic migration), or massive (>10 cm and/or >50% intrathoracic migration).

Classifications of Failure

Findings at revision surgery were classified into six groups based on intraoperative examination at time of revision surgery and our hypothesis of sequence of events leading to recurrence (Fig. 1):

1. Intact hiatus (fibrosis/tight hiatus).
2. 'Telescope' (Fig. 1a).
3. Paraesophageal hernia, often a lateral/posterior defect involving fundus with GOJ and wrap in position (Fig. 1b).
4. Crural failure with intact wrap herniation (Fig. 1c).
5. Crural failure with herniation and wrap disruption.
6. Wrap disruption only (intact hiatus and intra-abdominal position maintained).

The location of crural defects following primary surgery were classified into five groups based on intraoperative assessment at revision surgery: (a) intact hiatus, (b) lateral defect, (c) anterior defect only, (d) posterior defect only, or (e) anteroposterior defect (global).

Patients were routinely followed with subjective and objective review. Those who had not followed the routine clinical pathway were contacted for clinical review and examination. Symptoms were measured using the Gastrointestinal Quality of Life Index (GIQLI),[13] the modified Visick score,[14] the Dakkak dysphagia score,[15] the atypical reflux score,[16] and the satisfaction score. These were measured at <1 year, 1–3 years, 3–5 years, 5–10 years, and >10 years. Continuous data are presented as median (IQR). Paired *t*-test was used to calculate pre- and postsurgical scores. Statistical analysis was performed using the IBM SPSS, version 20.

RESULTS

Patient demographics and procedures

Two hundred eighty-four patients (126 male, 158 female) underwent revision surgery between 1992 and 2015. The median age was 57.1(42.5–65.3) years at primary surgery and 60.8 years (48.2–69.1) at revision surgery. The median interval between primary and revision surgery was 46.5 months (19.7–95.1). Primary surgery had been performed at the authors' institution in 121(43%) patients and 163(57%) at other institutions. The primary and revision procedures are shown in Table 1. Median postoperative follow-up was 122.8 months (75.3–180.3) after primary surgery and 91.55 months (40.5–152.5) after revision surgery. Revision surgery was performed open in 113(40%), laparoscopic conversion to open in 20(7%), and laparoscopic in 151(53%). Mesh reinforcement was used in

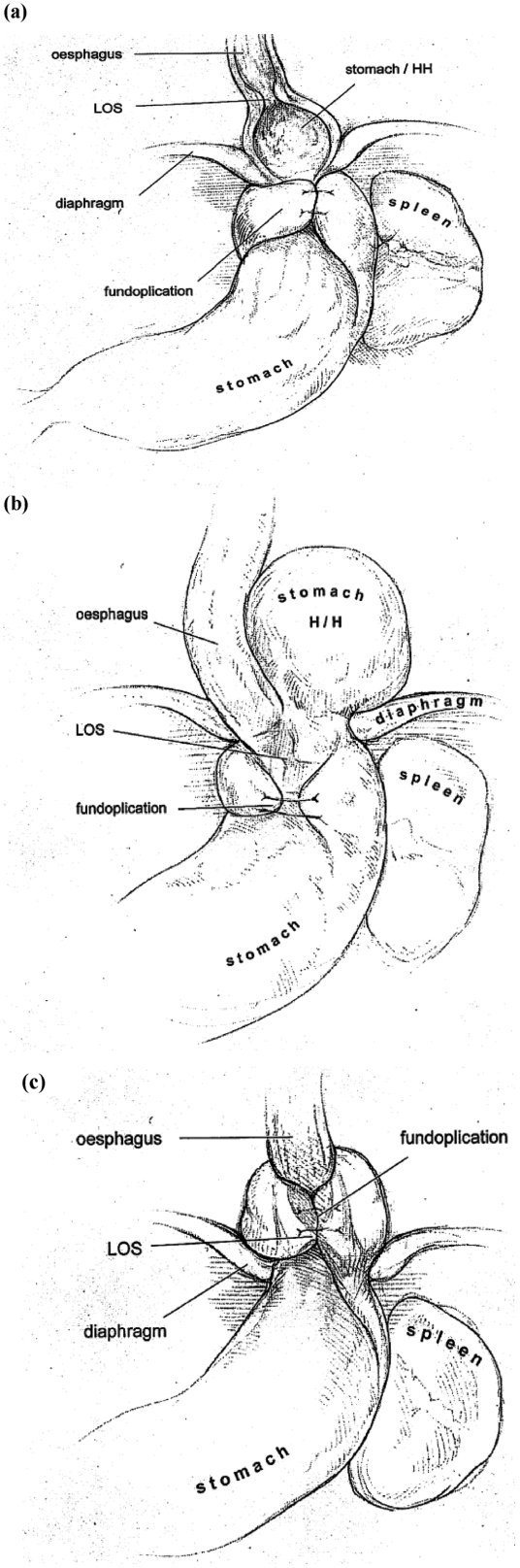


Fig. 1 Classification of types of hernia recurrence following primary. (a) Telescoping; (b) Paraesophageal hernia; (c) Crural failure and intact wrap herniation.

Table 1 Primary and revision procedures

Type of procedure	Primary surgery	Revision surgery
Lap 360	156	116
Open 360	86	94
Lap 270	4	1
Open 270		7
Lap 180	4	4
Open 180	1	14
Lap/open 360–270		3(Lap):3(O)
Lap/open 360–180		5(Lap):5(O)
Lap 270–360		4
Lap Dor		3
Hiatal repair only		2
Other		2
Not available	33	21
Total	284	284

Lap, laparoscopic; O, Open.

14(5%) and cut-Collis gastroplasty was performed in 36(13%) of revision operations. Intraoperative morbidity occurred in 56(19.7%), consisting of 27(9.5%) gastric perforations (11 requiring sutured gastrotomy and 16 required stapled wedge gastrectomy of the tip of the posterior fundoplication), esophageal perforation in 6(2.1%), pleural breach in 15(5.3%), and bleeding in 8(2.8%). 10(3.5%) patients were performed as emergency revision procedures, which was not associated with increase morbidity or recurrence or symptomatic failure.

Further revision surgery (re-revision) was required in 21 patients, 18 were elective and 3 emergencies. There was no change in re-revision rate over time. Esophagectomy was eventually required in two and gastrectomy in two patients. One patient had multiple previous repairs with subsequent recurrent reflux aspiration and severe esophageal dysmotility, which after 10 years culminated in elective esophagectomy and feeding jejunostomy. The second patient also had multiple previous repairs and was found to have at least a third of the esophagus grossly adherent to the diaphragm with mediastinal fibrosis, and had perioperative conversion to two-stage esophagectomy. Original pathology in both patients was a massive hiatus hernia. The two patients who required gastrectomy had multiple previous open repairs with intractable symptoms. There was no operative or 30-day mortality.

Findings at the revision procedure

The median time (years) to each recurrence type, in ascending order, was intact hiatus 1.3, paraesophageal 3.8(2.6–4.1), telescope 4.3(2.4–6.2), primary wrap disruption 4.4(1.2–9.5), crural failure with intact herniated wrap 4.4(4.6–7.9), and crural failure and wrap disruption 6.1(4.1–8.5). The types of recurrence intervals over time after primary surgery are shown (Table 2). The most common type at <1 year was 'telescoping' and wrap herniation in the remaining years.

Table 2 Type of recurrence at each time interval after primary surgery, *n*(%).Data were not available in 56 patients. Bold highlights the most common type of recurrence at each time interval

Type of recurrence	<1 year	1–3 years	3–5 years	5–10 years	>10 years	Total
Intact	0(0)	3(8.6%)	3(7.5%)	4(5.6%)	10(14.8%)	20
Telescope	**6(42.9%)**	6(17.1%)	6(15%)	11(15.5%)	9(13.2%)	38
Paraesophageal hernia	1(7.1%)	1(2.9%)	4(10%)	8(11.5%)	7(10.3%)	21
Crural failure and fundoplication herniation	4(28.6%)	**19(54.3%)**	**17(42.5%)**	**32(45.1%)**	**30(44.1%)**	102
Crural failure and fundoplication disruption	2(14.3%)	2(5.7%)	7(17.5%)	10(14.1%)	6(8.8%)	27
Fundoplication disruption	1(7.1%)	4(11.4%)	3(7.5%)	6(8.5%)	6(8.8%)	20
Total	14(100%)	35(100%)	40(100%)	71(100%)	68(100%)	228

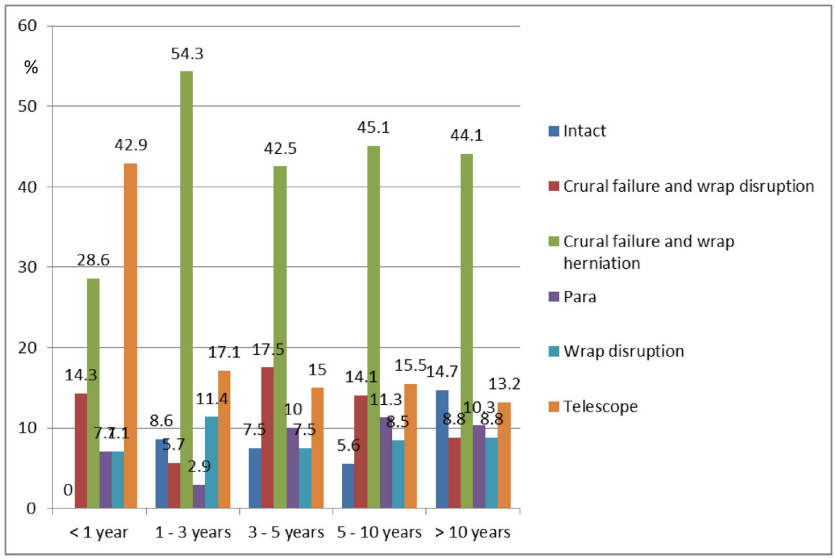


Fig. 2 Proportion (%) of types of recurrence seen at revision surgery (*y*-axis) at each time following primary surgery (*x*-axis).

The distribution of recurrence type at each interval is shown (Fig. 2).

Location of crural defect following primary surgery over time

The median time (in years) for location of crural defect, in ascending order, was intact hiatus 2.6 (1.1–7.3), anteroposterior 3.4(1.6–6.7), anterior only 5.1(2.3–9), and posterior 5.3(2.8–13.7). The distribution over time is shown (p = nonsignificant) (Table 3) (Fig. 3).

Recurrence following revision hiatal surgery

Median follow-up after revision surgery was 91.6 months (40.5–152.5). Seventy-two (25%) patients were lost to follow up (moved/deceased/unwell) and the remaining 212 patients had objective assessments within the last 3 years for recurrence (gastroscopy and/or swallow). Anatomical recurrence occurred in 44 patients giving a 15.4% recurrence rate of the whole series, and probably a 'true' recurrence rate of 20.7% in the 212 patients with objective investigations. Recurrences were subdivided by findings of size of hiatus hernia at primary surgery and size of hiatus hernia at revision surgery (Table 4). The majority of recurrences appeared to be following small hiatus hernia presence at primary surgery, but when individual groups were analyzed, there was no difference in the recurrence rates by size of primary hernia (Table 4, 3rd column]. Reflux symptoms were present in 57%(24/42) of the further recurrence group, compared to 26%(44/170) in those with no further recurrence. Re-revisions were performed in 21 patients and there was no difference in re-revision rate over time.

Quality of life following revision surgery

Prerevision and postrevision GIQLI scores were available in 154 patients giving 72% response rate of the 212 patients available to follow up and 54% response rate of the entire cohort (Table 6).

DISCUSSION

Revision surgery is reported technically difficult and associated with increased morbidity and decreased success compared to primary surgery.[3,7–11] A stringent process of patient selection was used for revision surgery in this series. The proportion of

Table 3 Proportion (%) location of crural failure at each time interval. Data were not available in 72 patients

Location	<1 year	1–3 years	3–5 years	5–10 years	>10 years	Total
Intact	4(36.3%)	11(33.3%)	8(20.5%)	10(15.4%)	13(20.3%)	46
Anterior	1(9.1%)	10(30.3%)	14(35.9%)	26(40%)	27(42.2%)	78
Posterior	1(9.1%)	2(6.1%)	5(12.8%)	10(15.4%)	8(12.5%)	26
Anteroposterior	5(45.5%)	10(30.3%)	11(28.2%)	15(23.1%)	15(23.4%)	56
Lateral	0(0%)	0(0%)	1(1.6%)	4(6.2%)	1(1.6%)	6

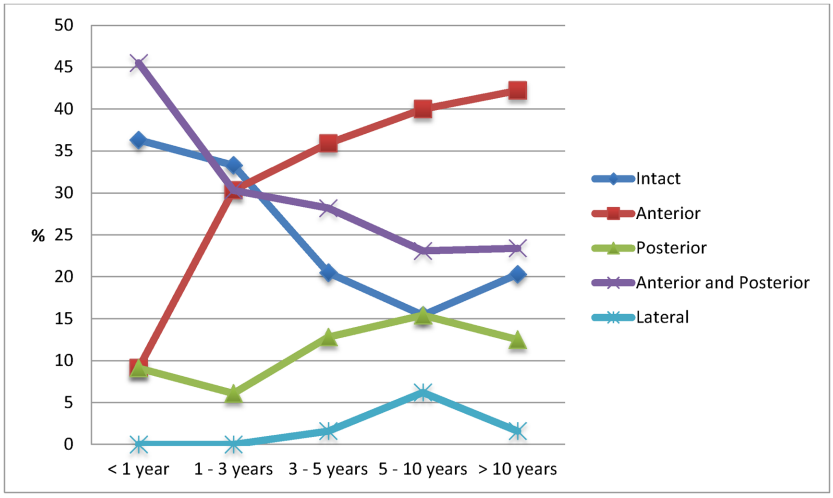


Fig. 3 Incidence of types of crural defects over time.

Table 4 The effect of primary hiatus hernia size on rates of recurrence after revision surgery

Hiatus hernia size at primary surgery	Recurrence following revision Surgery; *n*(% of all recurrences)	Recurrence rate by size of hernia
No hiatus hernia ($n = 25$)	5(11.4%)	5/25(20%)
Small ($n = 79$)	18(40.8%)	18/79(22.8%)
Large ($n = 66$)	12(27.3%)	12/66(18.2%)
Not available ($n = 45$)	9(20.5%)	9/45(20%)
Total recurrences in series	44(100%)	

revision procedures commenced as open surgery was high and reflected the policy of performing open revision surgery if primary surgery had been open. This approach was deliberate, to obtain a better repair and reduce intraoperative complications, especially in the early learning curve. Other studies have indirectly supported our caution, with reports of 30% esophagogastric perforation rate laparoscopic surgery[7,11] and up to 60% perforation rate in laparoscopic converted to open revision procedures,[11] although there is bias in the latter group as perforation is the likely cause of conversion. Surgeons undertaking revision procedures should still be well advised about the intraoperative morbidity, especially during early experience. Our overall conversion rate for revision surgery was 7% and similar to other series.[11] A recent systematic review of laparoscopic revision fundoplication concluded mean conversion rates between 5.6%–7.4% (0%–22%).[10]

Revision hiatal surgery is associated with substantial morbidity.[7,8] Our overall intraoperative morbidity was 20%, the most common event being gastric perforation (10%) and esophageal perforation (2%) with a lower incidence of pneumothorax and bleeding (1%–3% each), which is consistent with other reports of 13%–14% perforation and up to 6% pneumothorax.[7,8,10] A prospective record of postoperative complications was not available. There was no mortality. Two recent series on revision massive hiatus hernia surgery (using open abdominal, laparoscopic and open transthoracic approaches) have reported 33%(7/21) visceral perforation and 9.5%(2/21) leak rate;[7] and the other reported 37% operative morbidity and 1.9%(1/52) mortality from respiratory causes.[8] A systematic review summarized 18.6% intraoperative morbidity although individual studies have reported up to 50% complications, and mean postoperative complication rate of 16.9%.[10] Mortality, however, is low (0.3%) and mainly from respiratory causes.[10,11] Re-operation following revision surgery in our series was required in 21/284 (7.5%) and similar to that reported by Haider *et al.* (9.6%, 5/52)[8] and Juhasz *et al.* (10%, 2/21).[7] Two patients (0.7%) required esophagectomy and two required gastrectomy. It is also worth noting that two other authors report

proceeding directly to resection surgery in patients with previous multiple repairs in 10%.[7,9] The requirement for radical resection either as a result of complication or as a definitive procedure for functional outcome cannot be underestimated.

Temporal changes in type of recurrent hiatus hernia following primary surgery

This is the first study to investigate the changes in types of hiatus hernia recurrences over time. We used a classification which we hypothesized reflected the temporal sequence of events leading to recurrence. Telescoping of the cardioesophageal junction through the intact hiatus and fundoplication is an early event, possibly as a result of mechanical forces on an otherwise robust, and still intact antireflux apparatus. Paraesophageal hernia type recurrence, is also seen to be an early event, and may be caused by a small posterior-lateral defect from inadequate crural closure, or loose redundant left-sided fundoplication. Crural weakening with a widening hiatus may occur later, possibly due to prolonged exposure to mechanical stressors and intraabdominal pressures.[17] Theoretically, once the hiatus is weakened, the same pressures may push the entire fundoplication assembly progressively caudally leading to intrathoracic migration, or a sudden increase in intraabdominal pressure may lead to more sudden migration of the whole apparatus. Finally, the wrap itself may become disrupted, leading to disassembly of the entire apparatus. This hypothesis was partly borne out in our results where the most common recurrence type in the first year was 'telescoping', which accounted for 40% of all recurrences and then decreased over the subsequent years, with the shortest median time to recurrence (4.3 years). Surgical strategy may be devised to counter this tendency. The early telescoping phenomenon emphasizes the need to stabilize the esophagus within the wrap, and the entire apparatus below the diaphragm, if possible. We perform this using a modified cardiopexy, securing the cardioesophageal junction and posterior wrap to the median arcuate ligament.[21]

Fundoplication wrap herniation was the most common overall type of failure. It was also the second most common type of early failure. The many early migrations occurring at the start of the laparoscopic learning curve probably reflects inadequate crural closure. Wrap migration was also the most common type of recurrence in the later part of the study, especially at 5–10 years and >10 years, probably reflects true physiological weakening of the crus. Several other studies, while not succinctly describing the 'types' of failures, similarly report intrathoracic 'migration' as the most common type of recurrence ranging from 44% to 75%, followed by telescoping 12%–16%, paraesophageal hernia 15% and wrap disruption 6%–16%[7,10,11,18–20] although none of these studies have demonstrated variation in types and frequency over time.

Table 5 The effect of size of initial recurrence on revision failure

Recurrent hiatus hernia size seen at revision surgery	Recurrence following revision surgery; *n*(% of all recurrences)	Recurrence rate by size of hernia
No hiatus hernia ($n = 28$)	7/44(15.9%)	7/28(25%)
Small or moderate ($n = 91$)	18/44(40.9%)	18/91(19.8%)
Large/massive ($n = 79$)	15/44(34.1%)	15/79(19.0%)
Not available ($n = 17$)	4/44(9.1%)	4/17(23.5%)
Total recurrences in series	44(100%)	

Temporal changes in location of crural failure following primary surgery

This is the first study to investigate temporal changes in the location of crural defects after primary surgery. The assessment was performed intraoperatively by senior author (GLF). The intact crura noted in 33%–36% of revisions performed within the first 3 years after primary surgery reflects early revision surgery for dysphagia rather than true crural failure. True crural failure in this period was usually a global anteroposterior defect, caused by early technical failure or postoperative vomiting, which occurred less frequently over time. This type of failure decreased over time while isolated anterior defects increased and became the predominant cause of failure beyond 5 years. This anterior failure, rather than the traditional view of posterior failure where sutures are traditionally placed, could be caused by deterioration of the central tendon of the diaphragm leading to loss of integrity of anterior fibrous tissue over time. A recent large experience of large hiatus hernia has made obvious the development of the central tendon defect, which occurs in patients developing giant hiatus hernia over many years.[21,22] The clinical implication of delayed anterior failure suggests emphasis be placed on a concurrent anterior repair, in addition to the traditionally held posterior repair, with a view to reduction in late recurrence.

Further recurrence after revision surgery

There was good follow-up of 212/284, considering the age at revision surgery and subsequent median follow-up of 7.6 years[9,11] but outcomes/responses can be influenced by follow-up duration.[23] We attempted objective testing on all patients as there is increased hernia recurrence rate in screened population compared to unscreened populations.[1,2] The recurrence rate was lower in unscreened population(15%) and

Table 6 Prerevision versus postrevision surgery scores. Visick, Dysphagia, and Components of GIQLI scores (paired t-test)

Outcome	Mean pre (SD)	Mean post (SD)	*P*-value
Visick score	3.27 (0.83)	2.37 (1.17)	**0.000012**
Dysphagia score	23.15 (9.90)	32.81 (10.54)	**0.000004**
Atypical reflux symptom score	23.69 (11.36)	15.35 (11.24)	**0.000001**
Satisfaction	0.88 (1.05)	2.16 (0.79)	**0.000001**
Symptom (GIQLI)	47.32 (11.45)	51.37 (12.98)	0.837161
Emotional(GIQLI)	10.6 (4.44)	13.10 (4.44)	**0.000001**
Physical (GIQLI)	11.58 (6.74)	14.64 (7.21)	0.143187
Social (GIQLI)	10.51 (3.70)	11.91 (4.34)	0.110152
Medical treatment (GIQLI)	2.65 (1.29)	3.01 (1.41)	0.653474
Question 27 (regurgitation)	2.04	2.61	**0.022**
Question 35 (heartburn)	2.39	2.69	0.154

GIQLI, Gastrointestinal Quality of Life Index.

higher in our screened population(20%) and lower when compared to other studies.[7,8,9,18] This is not strictly comparable as these studies have a select population of large recurrent hiatus hernias but with shorter follow-up. Despite expectation of a higher recurrence rate in patients with initially large hernia, neither hiatal hernia size at primary surgery nor size at revision surgery predicted recurrence after revision surgery (Tables 4 and 5). Patients with anatomical recurrence had double the symptom rate compared with those without recurrence, but it also worth noting than half of those with recurrence were asymptomatic and few required surgery. Those with symptomatic recurrences were manageable with the majority of 'symptoms' being dyspeptic. Hence, many recurrences and symptoms can be managed nonsurgically, with studies including ours, reporting less than half of recurrences requiring surgery.[4,24]

Quality of life

QOL questionnaires were posted to patients who had not followed our follow-up schedule leading to a high response rate of 72% compared with other studies.[11] There was significant improvement in Visick score, dysphagia score, atypical reflux symptom score, and satisfaction score following revision surgery but no change in the components of the GIQLI (Table 6). This is probably because the GIQLI 'symptom' domain incorporates many abdominal symptoms (e.g. diarrhea) resulting in less specificity for reflux symptoms alone, in contrast to specific Visick and Dysphagia scores. When symptom-specific questions of the GIQLI were analyzed, there was significant improvement in Question 27(for regurgitation) and a nonsignificant improvement in Question 35 (for heartburn) following revision surgery. This suggests only certain components of the GIQLI, but not the overall GIQLI score, are sensitive for hiatus symptomology. Different studies have used various outcome measures and all have reported 'success' especially in satisfaction. Revision surgery appears to achieve good satisfaction (although not as good as primary surgery).[3,4]

CONCLUSION

Hiatus hernia recurrence and crural defects, especially anterior crural defects, increase variably over time, raising speculation about the mechanism of hiatus hernia recurrence being deficiency of the central tendon in later time periods. This raises the possibility of alteration in surgical repair strategy. Telescoping occurs early and may be reduced by utilizing a composite cardiopexy repair and fundoplication where cardioesphageal junction is fixed to median arcuate ligament. Anterior repair of the central tendon in the larger hiatus hernia may be beneficial in preventing late recurrence. Revision hiatus hernia surgery is associated with significant intraoperative morbidity, but with adequate preoperative counseling and patient selection, can achieve improved quality of life and reasonable recurrence rates.

References

1 Rathore M A, Andrabi S I, Bhatti M I, Najfi S M, McMurray A. Metaanalysis of recurrence after laparoscopic repair of paraesophageal hernia. JSLS 2007; 11: 456–60.
2 Mehta S, Boddy A, Rhodes M. Review of outcome after laparoscopic paraesophageal hiatal hernia repair. Surg Laparosc Endosc Percutan Tech 2006; 16: 301–6.
3 Nason K S, Luketich J D, Qureshi I *et al.* Laparoscopic repair of giant paraesophageal hernia results in long-term patient satisfaction and a durable repair. J Gastrointest Surg 2008; 12: 2066–75.
4 Latzko M, Borao F, Squillaro A *et al.* Laparoscopic repair of paraesophageal hernias. JSLS 2014; 18: e2014.
5 Jay A P, Watson D I. Changing work patterns for benign upper gastrointestinal and biliary disease: 1994-2007. ANZ J Surg 2010; 80: 519–25.
6 Finlayson S R, Birkmeyer J D, Laycock W S. Trends in surgery for gastroesophageal reflux disease: the effect of laparoscopic surgery on utilization. Surgery 2003; 133: 147–53.
7 Juhasz A, Sundaram A, Hoshino M, Lee T H, Mittal S K. Outcomes of surgical management of symptomatic large recurrent hiatus hernia. Surg Endosc 2012; 26: 1501–8.

8 Haider M, Iqbal A, Salinas V, Karu A, Mittal S K, Filipi C J. Surgical repair of recurrent hiatal hernia. Hernia 2006; 10: 13–19.
9 Wennergren J, Levy S, Bower C *et al.* Revisional paraesophageal hernia repair outcomes compare favorably to initial operations. Surg Endosc 2015; 30: 3854–60.
10 van Beek D B, Auyang E D, Soper N J. A comprehensive review of laparoscopic redo fundoplication. Surg Endosc 2011; 25: 706–12.
11 Smith C D, McClusky D A, Rajad M A, Hunter J G. When fundoplication fails:redo? Ann Surg 2005; 241: 861–9.
12 Falk G L, Beattie J, Ing A *et al.* Scintigraphy in laryngopharyngeal and gastroesophageal reflux disease: a definitive diagnostic test? World J Gastroenterol 2015; 21: 3619–27.
13 Eypasch E, Williams J I, Wood-Dauphinee S *et al.* Gastrointestinal quality of life index: development validation and application of a new instrument. Br J Surg 1995; 82: 216–22.
14 Visick A H. A study of the failures after gastrectomy. Ann Coll Surg Engl 1948; 3: 184–226.
15 Dakkak M, Bennet R J. A new dysphagia score with objective validation. J Clin Gastroenterol 1992; 14: 99–100.
16 Belafsky P C, Postma G N, Koufman J A. The validity and reliability of the reflux symptom index (RSI). J Voice 2002; 16: 274–7.
17 Akimoto S, Nandipati K C, Kapoor H *et al.* Association of Body Mass Index (BMI) with Patterns of Fundoplication Failure: Insights Gained. J Gastrointest Surg 2015; 19: 1943–8.
18 Dallemagne B, Arenas Sanchez M, Francart D *et al.* Long-term results after laparoscopic reoperation for failed antireflux procedures. Br J Surg 2011; 98: 1581–7.
19 Soper N J, Dunnegan D. Anatomic fundoplication failure after laparoscopic antireflux surgery. Ann Surg 1999; 229: 669–76.
20 Horgan S, Pohl D, Bogetti D, Eubanks T, Pellegrini C. Arch Surg 1999; 134: 809–15.
21 Le Page P A, Furtado R, Hayward M *et al.* Durability of giant hiatus hernia repair in 455 patients over 20 years. Ann R Coll Surg Engl 2015; 97: 188–93.
22 Luketich J D, Nason K S, Christie N A *et al.* Outcomes after a decade of laparoscopic giant paraesophageal hernia repair. J Thorac Cardiovasc Surg 2010; 39: 395–404.
23 Dallemagne B, Kohnen L, Perretta S, Weerts J, Markiewicz S, Jehaes C. Laparoscopic repair of paraesophageal hernia. Long-term follow-up reveals good clinical outcome despite high radiological recurrence rate. Ann Surg 2011; 253: 291–6.
24 Hashemi M, Peters J H, DeMeester T R *et al.* Laparoscopic repair of large type III hiatal hernia: objective follow-up reveals high recurrence rate. J Am Coll Surg 2000; 190: 553–60.

Royal College of Surgeons
ADVANCING SURGICAL CARE

ONLINE CASE REPORT

Ann R Coll Surg Engl 2016; **98:** e103–e105
doi 10.1308/rcsann.2016.0154

Recurrence after composite repair of a giant hiatus hernia: 'the golf club' deformity is a distinctive clinical and radiological picture

RV Furtado[1], GL Falk[1–3], SJ Vivian[2]

[1]Concord Repatriation General Hospital, Sydney, Australia
[2]Sydney Heartburn Clinic, Lindfield, Australia
[3]Macquarie University, Sydney, Australia

ABSTRACT

BACKGROUND Recurrence of a hiatus hernia after cardiopexy repair can obstruct the lower oesophagus but also provide characteristic radiographic images after a barium meal.

CASE HISTORY Two patients with recurrence of a hiatus hernia underwent repeat surgery. Here, we provide and discuss diagnostic imaging, surgical findings and outcome for these male and female patients.

CONCLUSIONS Repeat surgery is indicated in patients with recurrence of a hiatus hernia after repair.

KEYWORDS
Hiatus hernia – PEH – Recurrence – Composite repair

Accepted 10 July 2015

CORRESPONDENCE TO
Gregory Falk, E: sydney.heartburn@gmail.com

A recurrent hiatus hernia after repair of a massive hiatus hernia can present in several ways (a telescoping recurrence, a para-oesophageal recurrence, or a sliding hiatus hernia of the cardio-oesophageal junction (COJ)) and can have a complex appearance on barium studies.[1] A composite fundoplication failure may present a different picture.[2]

Repair methods have been reported by Russell[3] and Menguy[4] but, currently, few surgeons use such methods.[5,6] Repair can be managed only through surgery. A characteristic appearance is observed after a barium meal. Awareness of the potential presentation and imaging appearance may help management.

Case History

A giant hiatus hernia with symptoms of chronic volvulus ('para-oesophageal hernia') was repaired in a 77-year-old male (patient 1) by laparoscopy. The diaphragmatic hiatus was repaired using 0-Ethibond (Ethicon, Somerville, NJ, USA). A composite repair with cardiopexy and fundoplication was done (Fig 1) according to a method reported previously.[7]

Four months after surgery, dysphagia occurred and was associated with haematemesis. Emergency gastroscopy demonstrated two ulcers in the herniated stomach. The main body of the stomach could not be entered due to angulation. Barium swallow showed acute angulation at the COJ, with reherniation of the anterior aspect of the fundoplication into the thorax (Fig 2 and 3). Laparotomy demonstrated anterior hiatal failure, with the anterior fundoplication herniated into the chest. However, the COJ was held down by cardiopexy, which generated torsion and obstruction.

Surgical repair of a 40% PEH was undertaken in a similar manner in a 66-year-old female (patient 2) suffering from heartburn, regurgitation, early satiety, dyspnoea, and episodes of pulmonary aspiration. She presented to our unit

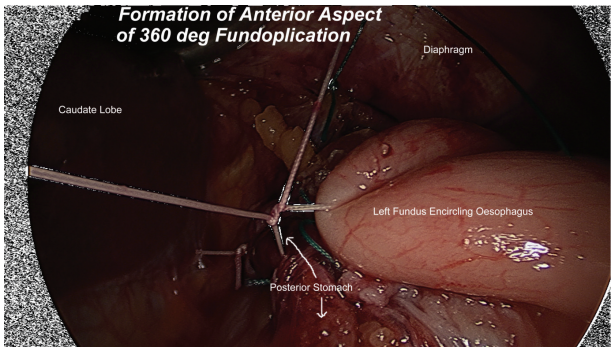


Figure 1 Construction of the composite fundoplication

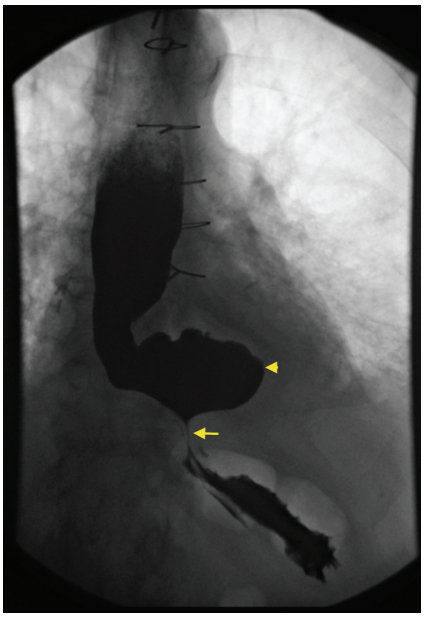


Figure 2 Erect, anteroposterior barium oesophagogram showing a recurrent hiatal hernia in patient 1. The body of the stomach has telescoped through the wrap (arrow) to lie within the chest (arrowhead). The image suggests that the cardio-oesophageal junction is in the mediastinum, but this appearance did not correspond with surgical findings.

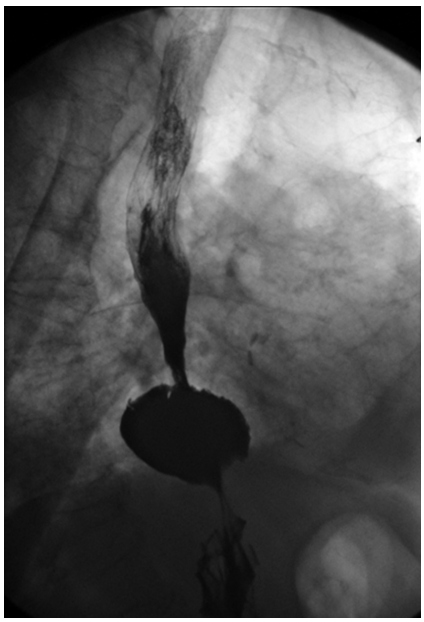


Figure 3 Erect, lateral barium oesophagogram in patient 1 showing a characteristic 'golf club' appearance.

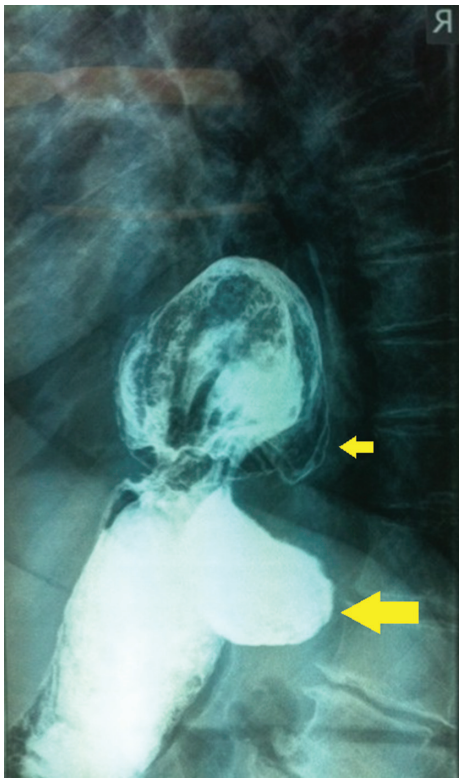


Figure 4 Erect lateral barium oesophagogram of patient 2 showing recurrence of a hiatal hernia. The cardio-oesophageal junction appears to be in the mediastinum (small arrow). The posterior fundoplication wrap is intact (large arrow) but anterior failure of the hiatus is noted.

again 6 months later with epigastric pain and early satiety after eating, and had dysphagia. The endoscope could not pass the COJ but barium studies showed a distinct appearance (Fig 4). At revision surgery, anterior failure of the hiatus and anterior reherniation of the fundoplication was demonstrated. The cardiopexy remained *in situ* in the abdomen and generated torsion.

Discussion

In some patients, anterior failure of hiatal repair and persistence of the cardiopexy can result in obstruction. Severe obstruction of the oesophagus or upper stomach necessitates revision surgery. Radiography demonstrates oesophageal filling with gastric bubbles on the bottom reminiscent of a 'golf club'. If this feature is seen, anterior failure of the hiatus and reherniation of the anterior portion of the 360° fundoplication should be expected. Dysphagia and obstruction are indications for surgical repair rather than medical management. Dilatation is not indicated because it is impractical and because symptoms arise due to axis deviation (which stop passage of the gastroscope) and not a stenosis.

FURTADO FALK VIVIAN

RECURRENCE AFTER COMPOSITE REPAIR OF A GIANT HIATUS HERNIA: 'THE GOLF CLUB' DEFORMITY IS A DISTINCTIVE CLINICAL AND RADIOLOGICAL PICTURE

References

1. Smith GS, Isaacson JR, Draganic BD, Baladas HG, Falk GL. Symptomatic and radiological follow-up after para-esophageal hernia repair. *Dis Esophagus* 2004; **17**: 279–284.
2. Gibson SC, Wong SK, Dixon AC, Falk GL. Laparoscopic repair of giant hiatus hernia: prosthesis is not required for successful outcome. *Surg Endosc* 2013; **27**: 618–623.
3. Russell COH. Median arcuate ligament repair for gastro-oesophageal reflux (Hill repair). In: Jamieson GG, ed. *Surgery of the Oesophagus*. Edinburgh: Churchill Livingstone; 1988. pp. 261–266.
4. Menguy R. Composite repair for gastro-oesophageal reflux. In: Jamieson GG, ed. *Surgery of the Oesophagus*. Edinburgh: Churchill Livingstone; 1988. pp.267–270.
5. Aly A, Munt J, Jamieson GG *et al*. Laparoscopic repair of large hiatal hernias. *Br J Surg* 2005; **92**: 648–653.
6. Low DE, Unger T. Open repair of paraesophageal hernia: reassessment of subjective and objective outcomes. *Ann Thorac Surg* 2005; **80**: 287–294.
7. D'Netto TJ, Falk GL. A technique for the laparoscopic repair of paraoesophageal hernia without mesh. *J Gastrointest Surg* 2014; **18**: 851–857.

Diseases of the Esophagus (2004) **17**, 279–284

DISEASES OF THE ESOPHAGUS

Original article

Symptomatic and radiological follow-up after para-esophageal hernia repair

G. S. Smith,[1] J. R. Isaacson,[1] B. D. Draganic,[2] H. G. Baladas,[1] G. L. Falk[1]

[1]*Department of Surgery, Concord Repatriation General Hospital, Hospital Road, Concord and* [2]*Department of Surgery, John Hunter Hospital, Lookout Road, New Lambton NSW, Australia*

SUMMARY. **The treatment of para-esophageal hernia by the laparoscopic approach has been described by a number of authors. The lower morbidity of the laparoscopic approach compared with the open approach holds some attraction, however, reservations regarding the durability of laparoscopic repair exist. There is a paucity of objective follow-up data in the literature with regard to repair durability and symptomatic outcome. A review was undertaken of 94 patients over a 7 year period undergoing attempted laparoscopic repairs of para-esophageal hernia. Preoperative and operative data was collected and patients underwent postoperative interview and barium meal. Laparoscopic repair was successfully completed in 86 patients. Symptomatic reherniation occurred in 12% (10/86) of patients undergoing laparoscopic repair. These patients underwent open reoperative surgery. There were no symptomatic recurrences in patients undergoing initial open repair. Symptomatic outcome was assessed by interview in 78% (73/94) of patients at a median of 27 months (3–93 months) postoperatively. Ninety-seven percent (71/73) of patients were satisfied with their ultimate symptomatic outcome however, this group included seven patients who had required reoperative surgery for symptomatic recurrence and were therefore laparoscopic failures. In order to determine the asymptomatic recurrence rate patients were requested to undergo a barium meal. A further nine small asymptomatic recurrences were diagnosed in 42 patients having had laparoscopic repair. This represents an asymptomatic radiographic recurrence rate of 21%. Laparoscopic repair in this series was associated with a 12% symptomatic recurrence rate. The majority of patients with symptomatic recurrence underwent open reoperation with good results. Strategies for reducing recurrences should be examined in prospective series.**

KEY WORDS: **laparoscopy, para-esophageal hernia.**

INTRODUCTION

The treatment of para-esophageal hernias (PH) presents a difficult surgical challenge. Long-term objective anatomical follow-up is scarce in both the open and laparoscopic literature. Traditionally, however, PH repair has been associated with a high recurrence rate. A variety of operative techniques including hernia sac dissection, esophageal lengthening and prosthetic hiatal repair have been suggested to minimize hernia recurrence.

The aim of this study was to evaluate symptomatic outcome and integrity of repair in 94 patients undergoing attempted laparoscopic repair of PH.

Address correspondence to: Dr Garett Smith, Department of Surgery, Royal North Shore Hospital, St Leonards 2065, Sydney NSW, Australia. Email: gssmith@doh.nsw.gov.au

MATERIALS AND METHODS

Ninety-four patients undergoing attempted laparoscopic repair of PH within a single consultant service between April 1992 and March 1999 were reviewed. Included in this series were patients with symptomatic herniation of the gastric fundus through the esophageal hiatus, above the gastroesophageal junction (GEJ) and into the mediastinum. This included all patients with a type 2 or type 3 hernia. Where the GEJ was not able to be returned to its infra-diaphragmatic position following esophageal mobilization, an esophageal lengthening procedure was performed.

Patients having had previous hiatal surgery and patients undergoing elective open repair over the study period were excluded from this series.

Details of presenting symptoms, preoperative investigations and operative procedures were obtained from case notes.

Postoperative interviews were conducted by a data manager. Postoperative Visick scores, dysphagia scores

and patient satisfaction scores were obtained. At the conclusion of the interview patients were asked to undergo a barium meal.

Operative technique

Surgery was performed by the senior author (GLF) and senior registrars undergoing post-fellowship training in laparoscopic surgery.

Operative Approach

The patients were placed in the modified lithotomy position with the operator between the patients' legs and the assistant on the patients' left. The laparoscope was introduced midway between the umbilicus and xiphisternum, slightly to the left of the midline. A straight viewing laparoscope was used. Early in the series, the left lateral hepatic segment was retracted using a hand held fan retractor, however, a fixed uniplanar hook retractor (Nathanson Liver Retraction System; Cook Medical Technology, Brisbane, Australia) is now used. Operating ports were placed in the left and right upper quadrants with an assistant's port in the left paraumbilical region (Fig. 1).

The sac was dissected from the crural pillars using ultrasonic shears (Ultracision Coagulating Shears; Ethicon Endo-Surgery Inc. Cincinnati, Ohio, USA) and from the mediastinum using a combination of sharp and blunt dissection. A nylon ribbon sling was placed around the distal esophagus. A small caliber Hurst Maloney rubber intraesophageal bougie was often used to aid in identification of the esophagus during dissection. The fundus was mobilized where necessary by division of short and posterior gastric vessels.

After reduction of the hernia, the sac was dissected from the anterior aspect of the GEJ and excized. A primary crural repair was performed posteriorly using heavy interrupted braided polyester sutures tied intracorporeally (0 Ethibond; Ethicon; Johnson and Johnson International, Brussels, Belgium). An anterior suture was used if required.

A short, loose Nissen-Rossetti fundoplication was performed and fixed to the crural pillars with braided polyester sutures (2/0 Ethibond; Ethicon; Johnson and Johnson International, Brussels, Belgium).

In two cases a partial anterior fundoplication was performed.

In patients where it was impossible to gain sufficient intra-abdominal esophageal length, a laparoscopic cut–Collis gastroplasty with fundoplication was performed as previously described.[1]

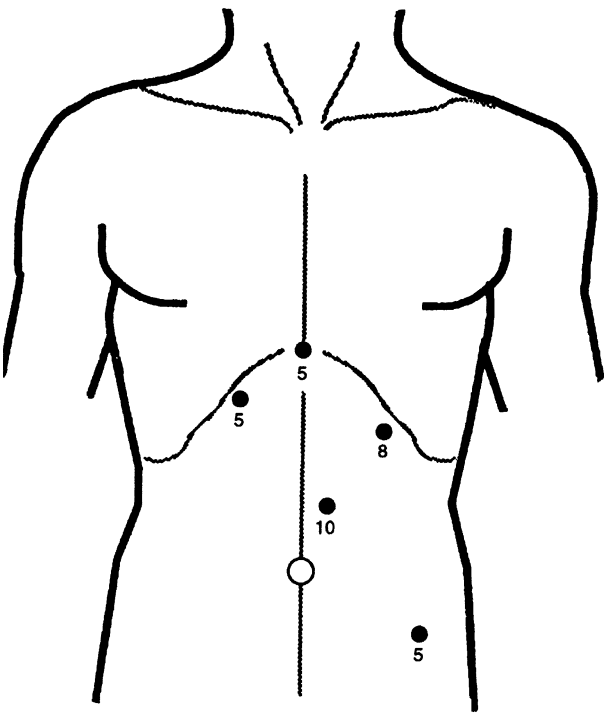


Fig. 1 Port placement for laparoscopic repair of paraesophageal hernia (PH). Port sizes in millimeters are shown.

RESULTS

A consecutive series of patients undergoing attempted laparoscopic PH between 1992 and 1999 was reviewed. The mean age was 65 years (15–95 years) and the male to female ratio was 35:59. The 30-day mortality was zero.

Preoperative symptoms

All patients were symptomatic. The predominant symptom was epigastric or retrosternal pain associated with eating. A small minority had reflux symptoms as the only presenting symptom however, almost half of the patients had reflux symptoms as part of their symptom complex. More than one quarter of patients presented with dysphagia. Approximately one-third of patients had symptoms not immediately associated with hiatus hernia by many clinicians, namely; shortness of breath, iron deficiency anemia, cough, constipation, palpitations and chest pain.

Preoperative investigations

All patients underwent either endoscopy, barium meal or both prior to surgery.

Endoscopy had been performed on 59 patients prior to referral to our unit. The presence of a PH was noted in 48 of these cases. In the remaining 11 patients, the endoscopist reported abnormal findings such as gastritis or petechial hemorrhages (nine cases) or reported no abnormality (two cases). The diagnosis in these cases was made on subsequent barium meal.

Barium meal was performed on 63 patients with 100% accuracy. Two patients had the diagnosis made on CT scan.

Preoperative manometry was performed on 66 patients. In 13 of these patients impaired esophageal motility was demonstrated. Preoperative dysphagia was reported in only four (31%) of these 13 patients. Fifty-three patients had normal preoperative peristalsis and 26 (49%) of these reported dysphagia preoperatively.

Lower esophageal sphincter measurements were only obtained in 26 patients due to difficulty passing the catheter through the distorted cardio-esophageal junction.

Ambulatory pH testing was carried out in 29 patients. Twenty-two of these patients complained of reflux symptoms, with 91% (20/22) having abnormal acid exposure. The remaining seven patients had no reflux symptoms, however, four of these had abnormal acid exposure (57%).

Operative procedures

Ninety-four laparoscopic repairs were attempted. In eight cases, repair was unable to be completed as a laparoscopic procedure and was completed as an open operation. In six cases, it was impossible to return the GEJ to its infra-diaphragmatic position without tension, and a laparoscopic cut–Collis gastroplasty was performed to increase esophageal length.

Postoperative symptomatic evaluation

Seventy-three of the 94 patients having had attempted laparoscopic repair were contacted for follow-up interviews (Table 1). Of the interviewed patients, 60 had undergone laparoscopic repair and fundoplication, six had initial laparoscopic repair converted to open surgery and seven had undergone re-operation for failed laparoscopic repair. The median postoperative interval to interview was 27 months (3–93 months). Patient satisfaction scores, pre- and postoperative Visick scores and dysphagia scores were recorded.

Patient satisfaction and Visick scores

At interview patients were asked if they were very satisfied, satisfied or not satisfied with their symptomatic outcomes. Postoperative Visick scores were recorded.

At interview the overall postoperative patient satisfaction rate was high with 97% (71/73) of patients satisfied with their ultimate symptomatic outcome. This group however, included seven patients who had undergone open reoperative surgery for symptoms following failed laparoscopic surgery. Only 89% (65/73) of patients therefore were satisfied with their laparoscopic repair. The most predominant postoperative symptoms were heartburn (10 patients) and increased flatus (10 patients). No patient reported an overall worsening of symptoms.

Postoperative dysphagia

A previously validated scoring system was used to evaluate postoperative dysphagia.[2] Two patients reported troublesome postoperative dysphagia with a further 10 recording occasional dysphagia for bread or meat.

Preoperative manometry had been performed on seven of these 12 patients, with three having dysmotility. Of these three, two underwent laparoscopic hernia repair and total fundoplication and one with absent peristalsis underwent laparoscopic hernia repair and posterior partial fundoplication.

Two patients reporting postoperative dysphagia had also complained of preoperative dysphagia. One had normal esophageal peristalsis demonstrated on manometry and both underwent laparoscopic repair and total fundoplication.

The operative procedures undertaken in the 12 patients reporting postoperative dysphagia were; six underwent standard laparoscopic repairs with total fundoplication, one patient with absent peristalsis on preoperative manometry underwent a laparoscopic posterior partial fundoplication, four had reoperative surgery, and one underwent open repair initially.

Postoperative anatomical evaluation

Known recurrences

Prior to telephone interview and barium meal, 10 of the 94 patients in this series had a known hernia recurrence (Table 2). All of these 10 patients had undergone laparoscopic repair initially. Eight had undergone open reoperative surgery.

Table 1 Postoperative symptomatic outcome

	Patient satisfaction		Visick (V) scores		Dysphagia scores	
Type of repair	Satisfied	Not satisfied	V1/V2	V3/V4	None or mild	Marked
Laparoscopic repair ($n = 60$)	59	1	58	2	59	1
Open reoperation following symptomatic recurrence ($n = 7$)	6	1	5	2	6	1
Conversion to open repair at initial surgery ($n = 6$)	6	0	6	0	6	0

Of the eight patients who had undergone reoperative surgery, six of seven contacted for post-reoperative interviews were satisfied with their ultimate symptomatic outcome and four reported dysphagia. Two of these patients had known small recurrences (both very satisfied, both reported mild dysphagia), and a further small recurrence in one patient was noted on post-interview barium meal and this patient although reporting dysphagia was satisfied with their symptomatic outcome.

Both patients who had not undergone reoperative surgery were very satisfied with symptomatic outcome and reported no dysphagia.

All patients in this series undergoing reoperative surgery for recurrence had undergone laparoscopic surgery initially. No reoperative surgery was performed laparoscopically.

Recurrences diagnosed following interview

Forty-seven of the 73 patients interviewed agreed to undergo a barium meal. Forty-two of these patients had undergone laparoscopic repair, three had undergone conversion to open repair and two had undergone open reoperative surgery following failed laparoscopic repair.

Hernia recurrences were identified in 11 of these patients, nine from the laparoscopic group and one each from the open conversion and reoperative group. These recurrences typically involved 2–4 cm of gastric herniation above the level of the diaphragm (Fig. 2). None of these patients were dissatisfied with their symptomatic outcome, although two reported occasional dysphagia.

DISCUSSION

The treatment of PH is difficult. Although the natural history of PH is incompletely understood, it is generally accepted that symptomatic hernias should be repaired due to the risk of progression to the life threatening complications of gastric volvulus dilatation or hemorrhage,[3] however, arguments for a conservative approach have been made.[4] Paraesophageal hernias occur predominantly in the elderly and may initially go undiagnosed prior to presentation with complications. Surgery for acute presentation is associated with high mortality and morbidity. The increasing availability of safe laparoscopic hiatal surgery in specialized units has led to an increase in patients referred for surgery where in the past they may have been considered unfit for major abdominal surgery.

The nomenclature of PH is confusing, being variously referred to as; rolling hernias, para-esophageal hernias, complicated hiatus hernias, upside down stomach, intrathoracic stomach or type 2, type 3 or type 4 hiatus hernias. Much of the inconsistency surrounding the nomenclature stems from disagreement as to the degree of herniation of the GEJ, which accompanies the gastric herniation. This confusion is further added to by the use of the terms *incarcerated* and *fixed* to describe the radiological appearance of these hernias.

Perhaps the classification that is most widely understood is that which describes four types of hernia; type 1, the sliding hernia characterized by upward dislocation of the cardia in the posterior mediastinum; type 2, the rolling or para-esophageal hernia characterized by upward dislocation of the gastric fundus alongside a normally positioned cardia; type 3, the combination sliding–rolling or mixed hernia characterized by upward dislocation of both the cardia and gastric fundus; and type 4, the hernia containing abdominal viscera in addition

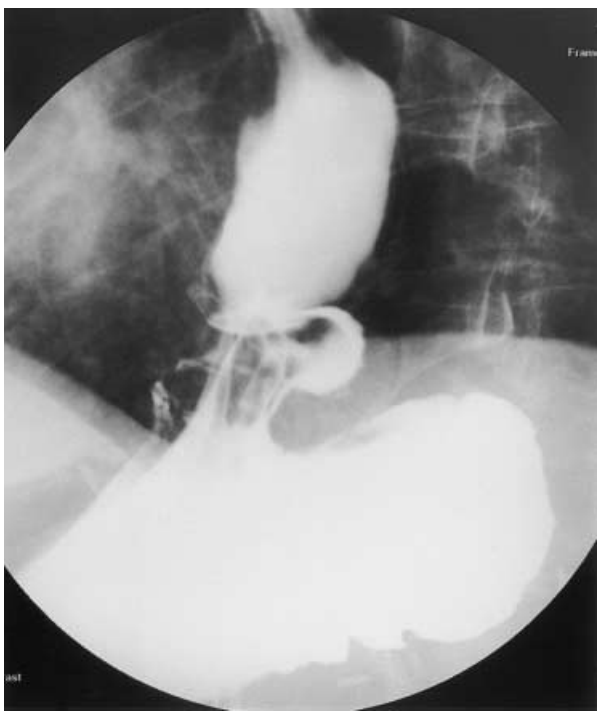


Fig. 2 Small asymptomatic hernia recurrence diagnosed on barium meal.

Table 2 Recurrence rates

	Laparoscopic repair	Open repair (initial)	Open repair (second)
Known recurrences prior to interview	10/86 (12%)	0/6 (0%)	–
Recurrences on barium meal – Post interview	9/42 (21%)	1/3 (33%)	1/2 (50%)

to the stomach. For the purposes of reporting this series we use the term PH to describe type 2, type 3 and type 4 hernias.

Knowledge of the pathology and a high index of suspicion are invaluable in making the diagnosis of PH. The diagnosis of PH was not appreciated at endoscopy in 12 patients. This may occur when the hernial neck is very wide and the crura attenuated resulting in vague and poorly appreciated crural impingement on the stomach at endoscopy. Subsequent barium meal was highly accurate and invaluable in establishing the degree of gastric herniation. Our current practice is to perform barium meal on all patients with a provisional diagnosis of PH.

The roles of preoperative manometry and pH testing are not well established. The passage of probes through the distorted cardio-esophageal junction is difficult and the distorted anatomy may lead to difficulty in interpretation. These investigations have the potential to alter surgical management if omission or modification of fundoplication is to be considered in those without evidence of reflux or in whom esophageal motility is disordered. Approximately half (46%) of our patients reported preoperative reflux symptoms and our approach is to perform fundoplication on all patients. A high rate of asymptomatic, demonstrable preoperative reflux and a significant rate of postoperative reflux in patients undergoing hiatal repair only support this approach.[5,6]

Operative approach

A good deal of controversy has surrounded the specifics of repair and a uniformly accepted and operative strategy for these hernias has yet to be established. The role of concomitant fundoplication, the role of esophageal lengthening procedures and the role of prosthetic mesh to reinforce or replace crural repair have been debated.

The success of these approaches is difficult to gauge, there being a paucity of large series with adequate follow-up or prospective comparative studies.

The technique for laparoscopic repair in this series consisted of reduction of the hernial contents, dissection of the hernial sac from the mediastinum and subsequent excision, posterior crural repair and fundoplication. The wrap was fixed to the crural repair posteriorly and to the diaphragm anteriorly and laterally.

Excision of the hernial sac from the mediastinal structures is technically challenging and places pleura and mediastinal structures at risk. Leaving the sac undissected, however, has been associated with a high rate of hernia recurrence.[7,8] In cases where reduction of hernial contents is difficult, sac dissection may facilitate this process. It is our experience that dissection of the sac in the extraperitoneal plane aids esophageal identification and dissection as well as allowing optimal posterior crural exposure. Once the sac has been dissected from the mediastinum it remains fixed at the anterior aspect of the GEJ. Care is required when dissecting the sac from this attachment to avoid perforation and vagal injury. Huntington describes a case of infarction of sac which had been left attached to the cardia following dissection from the mediastinum.[9]

For reasons discussed above, a fundoplication was performed routinely. Most frequently, this consisted of a Nissen-Rosseti fundoplication, which was fixed to the crura. Fundoplication obviated the need for a formal gastropexy to prevent intra-abdominal gastric volvulus.

Symptomatic follow-up

At interview 63 of 65 patients undergoing completed laparoscopic repair were satisfied with their ultimate symptomatic outcome. This group includes however, seven patients who required reoperative open surgery for symptomatic failure of repair. When this is taken into account, 88% (59/67) of patients had a satisfactory outcome following laparoscopic repair.

A number of patients who had undergone open reoperative surgery for laparoscopic failure expressed satisfaction with their overall outcome. These patients represent a symptomatic failure of laparoscopic repair. When this is taken into account 88% (59 of 67 patients) had a satisfactory outcome following laparoscopic repair.

Reoperative surgery for recurrence was associated with an inferior symptomatic outcome. Flatus and heartburn were the two most frequent postoperative symptoms. In this series significant post fundoplication dysphagia was uncommon.

Recurrence

The significant rate of symptomatic recurrence following laparoscopic repair of PH in this series is cause for concern. At reoperation there was failure of the hiatal repair as well as dislocation of the GEJ above the diaphragm. It is impossible to ascertain from these findings the mechanism for failure. In this series, where operative notes were reviewed retrospectively, no record was made of the dimensions of the enlarged hiatus, the proportion of stomach in the mediastinum or the preoperative position of the GEJ. It may be that the characteristics of the anatomical abnormalities associated with para-esophageal herniation predict the likelihood of recurrence. Indeed it would seem reasonable to assume that the primary crural repair of a grossly enlarged hiatus would be under more tension than a smaller

Table 3 Large series of laparoscopic para-esophageal hernia repair

Author	Patients	Anatomical follow-up	Recurrence rate (%)
Edye *et al*. 1998[7]	58	Dictated by symptoms	5/25 (20) without sac excision, 0/30 (0) with sac excision
Watson *et al*. 1999[8]	86	Nil stated	3/86 (3)
Huntington 1997[9]	58	Nil stated	0/57 (0)
Perdikis *et al*. 1997[10]	65	Barium esophagogram	7/46 (15)
Trus *et al*. 1997[11]	76	Nil stated	5/76 (7)
Gantert *et al*. 1998[12]	55	Nil stated	2/50 (4)
Swanstrom *et al*. 1999[13]	52	Nil stated	4/52 (8)
Pierre *et al*. 2002[20]	203	Nil stated	5/203 (2)

defect, and similarly, difficulty reducing the GEJ to its infra-diaphragmatic position may be associated with a higher recurrence rate. It is the authors' view that these issues will be clarified with the publication of comparative series utilizing various surgical approaches most particularly tension-free repairs of the hiatus and esophageal lengthening procedures. Further documentation of dimensions of the hiatal aperture, position of GEJ above the hiatus and proportion of stomach within the mediastinum will be important to document in prospective comparative series.

Recurrence rates in large laparoscopic series, defined as containing more than 50 patients, vary (Table 3).[7–14] This may reflect varying follow-up protocols.

Hashemi *et al*. reported a recurrence rate of 43% (9/21) in patients undergoing laparoscopic repair of type 3 hernias compared with 15% (3/20) of patients undergoing open repair.[15] They conclude that an open repair is the preferred approach.

Potential strategies for minimizing recurrence should be investigated. Strategies that have been recommended in laparoscopic series include sac dissection,[7,8] esophageal lengthening,[16] gastropexy and gastrostomy,[17,18] and prosthetic crural reinforcement with pledgets or patch.[19] Of these, only prosthetic patch reinforcement has been evaluated in a prospective randomized trial, which demonstrated a lower recurrence rate with prosthetic reinforcement of crural repair (0/17) than crural repair alone (3/18).[19]

The significance of small asymptomatic recurrences is unknown. While this may reflect failure of repair, progression to a clinically significant hernia has not been demonstrated. This is the subject of ongoing review.

This series is one of the largest published to date and is characterized by medium-term (27 months) follow-up in a high proportion of cases. While we have demonstrated that the majority of patients with a PH will be served well by laparoscopic repair and fundoplication, the rate of recurrence is significant. These results highlight the need for prospective evaluation of differing surgical approaches with the aim of increasing repair durability and improving symptomatic outcome.

References

1 Falk G L, Harrison R I. Laparoscopic cut Collis gastroplasty: a novel technique. Dis Esoph 1998; 11: 260–2.
2 Dakkak M, Bennett J R. A new dysphagia score with objective validation. J Clin Gastroenterol 1992; 14: 99–100.
3 Skinner D, Belsey R, Russell P. Surgical management of oesophageal reflux and hiatus hernia. J Thorac Cardiovasc Surg 1967; 53: 33–54.
4 Treacy P J, Jamieson G G. An approach to the management of para-oesophageal hiatus hernias. Aust NZ J Surg 1987; 57: 813–17.
5 Zaninotto G M, Costantini M. Anselmino M *et al.* Oesophageal and cardia function in patients with paraoesophageal hiatus hernia. Br J Surg 1997; 84: 1163–7.
6 Williamson W, Ellis F H, Streitz J M, Shahian D M. Paraesophageal hiatal hernia: is an antireflux procedure necessary? Ann Thorac Surg 1993; 56: 447–52.
7 Edye M, Salky B, Posner A, Fierer A. Sac excision is essential to adequate laparoscopic repair of paraesophageal hernia. Surg Endosc 1998; 12: 1259–63.
8 Watson D I, Davies N, Devitt P G, Jamieson G G. Importance of dissection of the hernial sac in laparoscopic surgery for large hiatal hernias. Arch Surg 1999; 134: 1069–73.
9 Huntington T R. Short-term outcome of laparoscopic paraesophageal hernia repair. A case series of 58 consecutive patients. Surg Endosc 1997; 11: 894–8.
10 Perdikis G Hinder R A, Filipi C J *et al.* Laparoscopic paraesophageal hernia repair. Arch Surg 1997; 132: 586–9; discussion 590–1.
11 Trus T L, Bax T, Richardson W S *et al.* Complications of laparoscopic paraesophageal hernia repair. J Gastrointest Surg 1997; 1: 221–8.
12 Gantert W A, Patti M G, Arcerito M *et al*. Laparoscopic repair of paraesophageal hiatal hernias. J Am Coll Surg 1998; 186: 428–32; discussion 432–3.
13 Swanstrom L L, Jobe B A, Kinzie L R, Horvath K D. Esophageal motility and outcomes following laparoscopic paraesophageal hernia repair and fundoplication. Am J Surg 1999; 177: 359–63.
14 Luketich J D Raja S, Fernando H C *et al.* Laparoscopic repair of giant paraesophageal hernia: 100 consecutive cases. Ann Surg 2000; 232: 608–18.
15 Hashemi M J, Peters H, DeMeester T R *et al.* Laparoscopic repair of large type III hiatal hernia: objective followup reveals high recurrence rate. J Am Coll Surg 2000; 190: 553–60; discussion 560–1.
16 Swanstrom L L, Marcus D R, Galloway G Q. Laparoscopic Collis gastroplasty is the treatment of choice for the shortened esophagus. Am J Surg 1996; 171: 477–81.
17 Medina L, Peetz M, Ratzer E, Fenoglio M. Laparoscopic paraesophageal hernia repair. J Soc Laparoendosc Surg 1998; 2: 269–72.
18 Oddsdottir M, Franco A L, Laycock W S, Waring J P, Hunter J G. Laparoscopic repair of paraesophageal hernia. New access, old technique. Surg Endosc 1995; 9: 164–8.
19 Frantzides C T, Richards C G, Carlson M A. Laparoscopic repair of large hiatal hernia with polytetrafluoroethylene. Surg Endosc 1999; 13: 906–8.
20 Pierre A F, Luketich J D, Fernando H C *et al*. Results of laparoscopic repair of giant paraesophageal hernias: 200 consecutive patients. Ann Thorac Surg 2002; 74: 1909–15; discussion 1915–16.

ORIGINAL ARTICLE

RE-OPERATION FOR FAILED ANTI-REFLUX SURGERY

J. K. LIM, E. MOISIDIS, W. S. MUNRO AND G. L. FALK

Department of Surgery, Concord, Strathfield and Sydney Adventist Hospitals, Sydney, New South Wales, Australia

Background: Between 1993 and 1995, 315 anti-reflux procedures were undertaken on our service. A previous anti-reflux procedure had been performed in 31 patients referred (10%). Previous surgery was, in the main (80%), a Nissen fundoplication.

Methods: Pre-operative investigations in all patients were manometry, 24 h pH monitoring, oesophagoscopy and barium radiology. On this basis the causes of failure of the previous surgery were established as hiatal failure in 20 (65%), unrecognized oesophageal dysmotility in three (10%) and fundoplication failure (slipped and disrupted) in eight (25%). Contrary to standard recommendations for re-operation most re-operative surgery was performed transabdominally (94%). Complications occurred in 16%.

Results: Review was undertaken at a mean of 21 months following surgery, and 91% of patients reported a good to excellent symptomatic outcome.

Conclusions: Transabdominal re-operative anti-reflux surgery has an acceptable complication rate and a surprisingly good symptomatic outcome in the medium term.

Key words: anti-reflux surgery, failed anti-reflux surgery, fundoplication, gastro-oesophageal reflux disease.

INTRODUCTION

Gastro-oesophageal reflux disease is a common disorder and despite recent advances in medical therapy that may offer symptomatic relief, anti-reflux surgery restores the functional integrity of the lower oesophageal sphincter, thus preventing acid reflux and its consequences.[1] The Nissen fundoplication has produced good results in more than 90% of patients for up to 10 years.[2] Surgery has achieved superior results to medical therapy alone.[3] Unfortunately, the excellent results following surgical management are not uniformly expressed, with up to 23% of patients experiencing recurrent, persistent or new symptoms in some studies.[4,5] Inadequate initial assessment of symptoms and aetiology, poor patient or procedure selection, and suboptimal surgical technique may in part explain this disparity.

Re-operation for gastro-oesophageal reflux is more technically difficult, potentially more hazardous and has less favourable results than the primary operation.[4] Unfortunately, many patients with failed anti-reflux surgery have not been adequately assessed prior to their initial operation, thus compounding difficulties in accurately identifying the cause of persistent symptoms. A thoracic approach has been frequently reported to achieve good results in re-operative anti-reflux surgery[6–8] although the abdominal approach has also been used with excellent results.[4,9]

The aim of this study was to determine the safety and outcome of the policy of re-operative abdominal surgery for symptomatic failure of a previous anti-reflux procedure.

Correspondence: G. L. Falk, PO Box 1085, Strathfield, NSW 2135, Australia.

Accepted for publication 18 June 1996.

METHOD

Between January 1993 and December 1995, 31 patients underwent remedial anti-reflux surgery. Surgery was performed by a single surgeon (GLF). All patients underwent endoscopy, manometry, 24 h pH monitoring and barium study prior to correctional surgery.

The case notes and operative reports of all the patients were reviewed. A telephone survey of patients, conducted by an independent observer (JKL), allowed operative results to be rated as excellent, good, unsatisfactory or failure. The principles of the modified Visick grade were applied to categorize patients.[10] Patients with excellent outcome were asymptomatic. A good result indicated minor digestive symptoms ameliorated by minor dietary measures or antacids. A poor result indicated recurrent reflux, hiatus hernia or intractable severe side effects.

RESULTS

The median age of the patients studied was 58 years (range 27–79). There were 15 male and 16 female patients. Primary surgery had been performed at another institution in 55% of patients. Reflux and regurgitation were the main indications for the primary anti-reflux procedure. Manometry or 24h pH studies had been performed in the 11 patients who underwent their initial procedure at our institution. The remaining patients did not undergo pre-operative investigation of oesophageal motility. Nissen fundoplication had been performed in 25 patients primarily, and a variety of other repairs in the remainder (Table 1). One primary procedure had been performed in 30 patients prior to revisional therapy and one patient had undergone two previous procedures.

Symptoms initiating further consultation were predominantly dysphagia and heartburn (Table 2). The time between the initial operation and the onset of symptoms suggestive of the loss of

Table 1. Type of previous repair

Previous repair	Patients (*n*)
Nissen fundoplication	25
Belsey IV	4
Collis–Nissen	1
Hill gastropexy	1
Total	31

Table 2. Symptoms indicating failure

Symptoms	Patients (*n*)
Heartburn/regurgitation	11
Dysphagia	17
Epigastric pain	9
Bloat	2

functional integrity of the fundoplication varied widely (recovery suite to 9 years). The patients who developed dysphagia postoperatively tended to present earlier than those complaining of recurrent reflux symptoms.

The primary anti-reflux procedure was laparoscopic in 18 and open in 13 patients. The most common reason for failure of the primary anti-reflux procedure in the series was identified as intrathoracic herniation of the fundoplication subsequent to hiatal failure ($n = 20$). A syndrome of early hiatal failure was identified in four patients following the introduction of laparoscopic fundoplication. This characteristically was associated with forceful regurgitation in the first 24 h after surgery, resulting in rupture of the hiatal repair and/or fundoplication sutures. In a further eight patients fundoplication failure resulted from slippage or disruption. Three patients were re-operated on for previously undiagnosed motility disturbances (Table 3).

Repair was performed via an abdominal approach in 29/31 (94%) patients, while two patients underwent a transthoracic repair. One of these patients had undergone two previous fundoplications and had hiatal fibrosis from a large gortex patch used to repair the hiatus. This required an Ivor–Lewis oesophagectomy. Three patients were re-operated on by laparoscopy and in each case the primary procedure had been laparoscopic. Floppy Nissen fundoplication was performed in 20 patients, Cut–Collis gastroplasty in four patients and partial fundoplication in six patients (Table 4).

The mean time to follow-up was 21 months. There was no mortality in the series. Morbidity was 16% (Table 5). One patient had a prolonged hospital stay requiring intensive care management of respiratory failure following resection of a gangrenous small bowel, secondary to postoperative small bowel obstruction.

Symptomatic patients only have been re-investigated. Persistent reflux on 24 h pH has been identified in one symptomatic patient. Excellent and good results have been reported by 28 patients (90%). Unsatisfactory results in the remaining three patients were due to reflux in one and dysphagia in two patients. Both patients with dysphagia had oesophageal dysmotility (amotile: 1; diffuse spasm: 1; Table 6).

Table 3. Cause of failure of initial surgery

Cause	Patients (*n*)
Hiatal failure	20 (3 para-oesophageal)
Wrap disruption	3
Slipped Nissen	5
Impaired oesophageal motility	3 (1 too tight)
Total	31

Table 4. Type of remedial surgery

Type	Patients (*n*)
Nissen fundoplication	20
Collis/fundoplication	4
Toupet	4
Belsey	2
Oesophagectomy	1
Total	31

Table 5. Postoperative complications

Type	Patients (*n*)
Wound infection	1
Adhesive small bowel obstruction	1
Wound pain	1
Pneumothorax	1
Impaired gastric emptying	1
Total	5

Table 6. Symptoms after re-operative anti-reflux surgery

Result	Patients (*n*)
Good to excellent	28
Unsatisfactory to poor	3
Heartburn/regurgitation (1)	
Dysphagia (2)	
Total	31

DISCUSSION

Re-operation after failed anti-reflux procedures is a surgical challenge. A higher rate of failure, morbidity and even mortality is to be expected. Morbidity rates of up to 28% in those undergoing re-operative anti-reflux surgery have been reported.[6]

The indications for re-operative anti-reflux surgery in the series were dysphagia and severe recurrent reflux that were resistant to medical therapy or dilatation. It has been the policy of the senior author (GLF) to re-operate in the presence of symptomatic recurrent herniation so that the complications associated with an intrathoracic fundoplication, such as ischaemia, perforation or massive haemorrhage, may be avoided.[11]

Review of the literature suggests that the most frequent

indication for re-operation has been recurrent reflux.[4,7,12] Our experience indicated hiatal failure to be the predominant mechanical problem leading to intrathoracic fundoplication. In four patients hiatal failure occurred as a result of severe postoperative vomiting in the recovery suite. This occurred in the early phase of laparoscopic anti-reflux surgery, also experienced by the Adelaide group,[13] and led to our modification of practice with the avoidance of opioid analgesics and the regular use of ondansetron to minimize postoperative vomiting. These measures have proven to be very effective, decreasing this problem to less than 2% of laparoscopic fundoplication procedures (G. L. Falk unpubl. data). Particular attention to measured hiatal closure at laparoscopy may contribute considerably to this lesser rate.

Recurrent reflux is usually due to mechanical wrap complications with either partial or complete wrap breakdown.[14,15] Dysphagia can occur as a result of too tight a wrap, intrathoracic migration or to a misplaced wrap (slipped Nissen). The association of both heartburn and dysphagia was seen in herniation of the repair into the chest and/or its location below the gastro-oesophageal junction (slipped Nissen).

Remedial surgery can be performed either via a thoracic[6] or an abdominal[4] approach. It was possible to perform 29 (94%) of the procedures via the abdominal route in this series. A Cut–Collis stapled gastroplasty was performed transabdominally in four cases to obtain an adequate intra-abdominal gastro-oesophageal junction for a shortened oesophagus.

Postoperative morbidity rates of 9 to 20% have been reported in the literature after primary surgery[2,15,16] with up to 30% after re-operations.[7,8] In our series there was no operative mortality, and a lower morbidity rate of 16%. We would attribute the low morbidity to the choice of a transabdominal approach as well as the concentration of expertise in a single service. Postthoracotomy pain was also avoided with the abdominal approach. A higher mortality and failure rate is associated with an increasing number of previous anti-reflux procedures.[6,8] The good to excellent outcome achieved in 90% of our patients probably reflects the fact that all but one patient (30/31) had previously undergone only one anti-reflux procedure.

CONCLUSION

Re-operative anti-reflux surgery in this series has been safe with an acceptable complication rate. This has been achieved by utilizing a transabdominal approach in all but two patients. Symptomatic results have been satisfactory in 90% of patients.

REFERENCES

1. Demeester TR, Johnson LF, Kent AH. Evaluation of current operations for prevention of gastro-oesophogeal reflux. *Ann. Surg.* 1974; **180**: 511–25.
2. Demeester TR, Bonavina L, Albertucci M. Nissen fundoplication for gastro-oesophageal reflux disease. Evaluation of primary repair in 100 consecutive patients. *Ann. Surg.* 1986; **204**: 2–9.
3. Spechler SJ, and the Department of Veterans Affairs Gastroesophageal Reflux Disease Study Group #277. Comparison of medical and surgical therapy for complicated gastroesophageal reflux disease in veterans. *N. Engl. J. Med.* 1992; **326**: 786–92.
4. Luostarinen ME, Isolauri JO, Koskinen MO *et al.* Refundoplication for recurrent gastroesophageal reflux. *World J. Surg.* 1993; **17**: 587–94.
5. Jamieson GG. The results of anti-reflux surgery and reoperative anti-reflux surgery—a review. *Gullet* 1993; **3**: 41–5.
6. Skinner DB. Surgical management after failed anti-reflux operations. *World J. Surg.* 1992; **16**: 359–63.
7. Martin CJ, Crookes PF. Reoperation for failed anti-reflux surgery. *Aust. N.Z. J. Surg.* 1990; **60**: 773–8.
8. Little AG, Ferguson MK, Skinner DB. Reoperation for failed anti-reflux operations. *J. Thorac. Cardiovasc. Surg.* 1986; **91**: 511–17.
9. Rieger NA, Jamieson GG, Britten Jones R, Tew S. Reoperation after failed antireflux surgery. *Br. J. Surg.* 1994; **81**: 1159–61.
10. Visick AH. Measured radical gastrectomy: Review of 505 operations for peptic ulcer. *Lancet* 1948; **1**: 505–10.
11. Richardson JD, Larson GM, Polk HC. Intrathoracic fundoplication for shortened esophagus. *Am. J. Surg.* 1982; **143**: 29–35.
12. Hatton PD, Selinkoff PM, Harford FJ. Surgical management of the failed Nissen fundoplication. *Am. J. Surg.* 1984; **148**: 760–3.
13. Watson DI, Jamieson GG, Devitt PG, Mitchell PC, Game PA. Paraoesophageal hiatus hernia: An important complication of laparoscopic Nissen fundoplication. *Br. J. Surg.* 1995; **82**: 521–3.
14. O'Hanrahan T, Marples M, Bancewicz J. Recurrent reflux and wrap disruption after Nissen fundoplication: Detection, incidence and timing. *Br. J. Surg.* 1990; **77**: 545–7.
15. Luostarinen M. Nissen fundoplication for reflux oesophagitis: Long term clinical and endoscopic result in 109 of 127 consecutive cases. *Ann. Surg.* 1993; **217**: 329–37.
16. Donahue PE, Samelson S, Nyhus LM, Bombeck CT. Floppy Nissen fundoplication. *Arch. Surg.* 1985; **120**: 663–8.

Conclusion

I had the good fortune to enter surgery at a time of gestalt change in the technology and direction of abdominal surgery. Many of the long and painful surgical procedures that involved opening of the abdominal cavity were progressively made redundant with the invention of laparoscopic surgical procedures. This had the fortunate effect of reducing the patient's pain and discomfort and length of stay in the hospital, with resultant cost-savings. It also provided better cosmetic results.

I helped to develop many of the techniques of oesophageal and upper laparoscopic surgery both in Australia and overseas. This resulted in multiple publications on refinements of laparoscopic techniques and review of surgical results. It also involved teaching the more junior and sometimes senior staff new approaches to laparoscopic techniques. Many of my junior colleagues were trained in my department and currently cover many of the teaching hospitals in Sydney and other surgical departments in Australia. This has given me a great sense of satisfaction and accomplishment.

Many of the techniques I developed have been adopted in this country and overseas. It has allowed me to collaborate with other surgeons in Australia through the Australian Cancer Study which has received international recognition in the publications listed in this section. My involvement with the surgical treatment of oesophageal carcinoma has resulted in numerous publications which have changed management of the disease. In recent years, I have been involved in supervising candidates for higher degrees in the sphere of oesophageal carcinoma and in the more prevalent manifestations of gastro-oesophageal reflux disease and its basic pathophysiology, diagnosis and treatment.

I believe that I have made a significant contribution in the surgical treatment of oesophageal cancer and in the other benign variants of oesophageal disease. This has extended from gastro-oesophageal reflux disease to oesophageal dysmotility, management of hiatus hernias and in the treatment of failed reflux and hiatal hernia surgery.