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Prognostic role of histologic tumour regression in patients receiving neoadjuvant chemotherapy for high-grade serous tubo-ovarian carcinoma

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Prognostic Role of Histologic Tumour Regression in Patients Receiving Neoadjuvant Chemotherapy for High-grade Serous Tubo-ovarian Carcinoma

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Research output from this thesis

Published manuscript

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Conference presentations

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Statement of contribution

This thesis originated from my employment at King Edward Memorial Hospital and subsequent research ideas were further developed in collaboration with my supervisors and other co-authors.

I have led the development of this thesis from 2016 including the obtainment of ethical approval, concept development, management of data collection, data validation, data analysis, and dissemination of research findings (development of manuscripts, posters, and verbal presentations). All co-authors have endorsed and acknowledged my level of contribution. *The Statement of Contribution of Others* for my publication is presented in Appendix 1.

Signed:

Dr Edwina Coghlan
Candidate

Dr Paul Cohen
Primary Supervisor

Date: 19 July 2018

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Abbreviations

BRCA1	breast cancer associated gene type 1
BRCA2	breast cancer associated gene type 2
CA-125	cancer antigen -125
CRS	chemotherapy response score
DNA	deoxyribonucleic acid
FIGO	International Federation of Gynaecology and Obstetrics
HGSOC	high-grade serous ovarian cancer
ICCR	International Collaboration on Cancer Reporting
IDS	interval debulking surgery
MDT	multi-disciplinary team
NACT	neo-adjuvant chemotherapy
OS	overall survival
PDS	primary debulking surgery
PFS	progression free survival
RMI	risk of malignancy index
STIC	serous tubal intraepithelial carcinoma
WA	Western Australia

Explanatory overview

High-grade serous tubo-ovarian carcinoma (HGSOC) is the most common tubal/ovarian malignant tumour and is usually diagnosed at an advanced stage. Historically, primary debulking surgery followed by adjuvant platinum-based chemotherapy was the recommended management of these patients. However, since two randomised controlled phase III trials (1, 2) both demonstrated non-inferior survival after neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS) compared to primary debulking surgery, there has been an increasing trend to treat HGSOC patients with NACT. (3, 4)

Evidence supporting the change in practice is mounting, with the findings of a recent meta-analysis of 1,607 women showing that NACT is associated with superior rates of optimal surgical cytoreduction, lower peri-operative mortality as well as post-surgical mortality, and better quality of life compared to primary surgery in patients with advance ovarian cancer. (5) A cross-sectional analysis that included more than 6000 women treated for advanced epithelial ovarian cancer in the United States, reported that adoption of NACT resulted in a sizable reduction in mortality within three years of diagnosis. (3)

Opinion, however, remains divided with calls for better methods of patient selection and improved efficacy of NACT. (6, 7) While histopathological scoring of tissue removed at IDS has been routinely used to measure the response to antineoplastic treatment for many solid tumours such as breast, (8-10) rectum (11, 12) and oesophagus, (13, 14) until recently, there has been no accepted system for HGSOC due to studies having small sample size, based on a single site, utilising differing classification systems and lacking in validation or reproducibility. (15-18)

Following a publication by Böhm at al., (15) who developed, tested and validated a three-tier 'Chemotherapy Response Score' (CRS) that was reported to be reproducible and easy for pathologists to use, the International Collaboration on Cancer Reporting (ICCR) recently recommended the adoption of this grading system, whilst calling for further studies to confirm its relevance. (19)

In response to the above, the purpose of this thesis was to test the hypothesis that the CRS score was independently associated with the survival outcomes of patients with advanced high-grade serous ovarian cancer undergoing NACT-IDS.

Study objectives

Testing the hypothesis that the CRS score is associated with the survival outcomes of patients with advanced ovarian cancer undergoing NACT-IDS" was assessed in two stages, each with their own objective:

First objective

- To externally validate the CRS scoring system as developed by Bohm et al. (15) and recommended by the ICCR for HGSOC patients.

Second objective

- To determine the prognostic significance of CRS with respect to progression free survival (PFS) and overall survival (OS) in patients with advanced HGSOC.

Thesis overview

This thesis provides a summary of the work undertaken to address the research objectives. It is divided into three chapters and is supported by a peer-reviewed publication (the candidate was first author on the publication).

Chapter 1: Literature review

Provides a literature review and a description of the anatomical location of the ovary, pathogenesis and aetiology of ovarian cancer, ovarian cancer staging and treatment regimens, and the significance of the chemotherapy response score.

Chapter 2: The chemotherapy response score for high-grade serous ovarian cancer patients treated with NACT and IDS

Addresses objectives one and two by exploring the clinical validity of the chemotherapy response score, the finding of which resulted in a publication and an oral presentation at an international conference.

Chapter 3: Discussion

Presents the final discussion and explores the overall strengths and limitations of work reported in this thesis and points to directions for future work in this area.

Chapter 1:

Literature review

1.1 Introduction

Ovarian cancer is the seventh most common cancer for incidence and mortality among women worldwide, accounting for an estimated 239,000 new cases and 152,000 deaths annually. (20) While age-standardised incidence rates have varied across the globe, higher rates have been observed in western countries than those seen in Asia and Africa. However, rates in higher-incidence countries have generally fallen while those from the lower-incidence countries have risen in recent decades, meaning the difference between countries is less marked than it was 30 years ago. (21) In Australia, ovarian cancer is the leading cause of gynaecologic cancer-related deaths (approximately 5% of all cancer deaths in women). In 2018, an estimated 1,613 Australian women will be diagnosed with ovarian cancer with 1,069 dying of the disease. (22)

For the few cases diagnosed early with localised tumour (Stage 1), the 5-year survival rate is 92% although the disease typically presents at a later stage, where the 5-year relative survival rate is less than 50%. Overall the 5-year relative survival rate generally ranges between 30% and 40% but has seen only very modest increases (2%–4%) since 1995. (23)

Family history is one of the most significant risk factors for ovarian cancer (24) with first-degree relatives of probands having a 3- to 7-fold increased risk, especially if multiple relatives are affected, and at an early age of onset. (25) More recent work has shown that 15-17% of patients diagnosed with HGSOC carry germline mutations in the BRCA1 and BRCA2 genes. (26)

Multiple other risk factors have been identified through epidemiological research within implicate hormonal and reproductive factors, such as age at menarche,

age at menopause, parity, lactation, (25, 27) oral contraceptive use, diabetes mellitus, body size, life style factors such as diet, alcohol consumption and physical activity (21) and benign gynaecologic conditions. (28, 29)

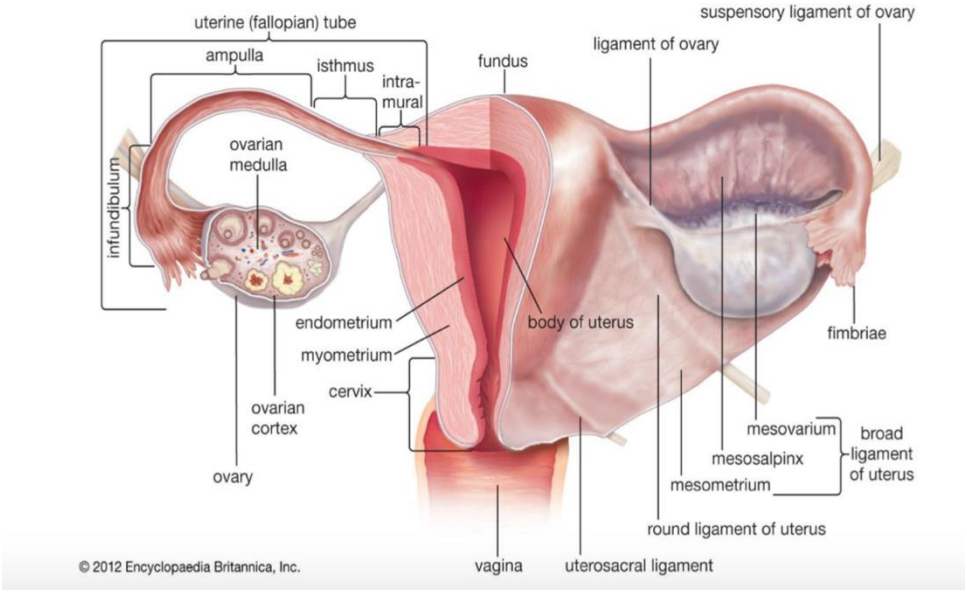
Women continue to experience non-specific symptoms such as back pain, fatigue, persistent abdominal pain, bloating or decreased appetite meaning that in the majority of cases affected women will present with disease at an advanced stage (30) (International Federation of Gynaecology and Obstetrics [FIGO] stage III and IV; see Table 1). (31) As a consequence, until researchers identify biomarkers that may enable early detection of HGSOC, this disease will continue to have a poor prognosis with limited treatment options.

1.2 Anatomy of the ovary and fallopian tubes

The ovaries are situated in the pelvis in close proximity to both the pelvic and abdominal organs (Figure 1). The ovary is the primary endocrine gland of the female reproductive system (32) and has two main functions (32):

- Oocyte production; and
- To secrete female sex hormones, oestrogen, progesterone, androgens and inhibin.

Figure 1. The female reproductive system. (32)



From: The Editors of Encyclopedia Britannica. Encyclopedia Britannica. Uterus Anatomy [Internet]. Encyclopedia Britannica. 2018 [cited 18 June 2018]. Available from https://www.britannica.com/science/uterus.

1.3 Pathogenesis and aetiology of ovarian cancer

The majority of benign and malignant ovarian tumours will originate from one of three cell types: epithelial cells, stromal cells or germ cells. (25) In developed countries, more than 90% of malignant ovarian tumours are epithelial in origin. (33). Epithelial ovarian cancer is a heterogeneous disease with histologic subtypes that differ in their cellular origin, pathogenesis, molecular alterations, gene expression, and prognosis. (21, 25, 34) Malignant epithelial ovarian cancer, the most common type of ovarian cancer, is comprised of five main histological types: high-grade serous (HGSOC; 70%), endometrioid (10%), clear cell (10%), mucinous (3%) and low-grade serous (<5%). (35, 36)

The cellular origin and pathogenesis of HGSOC is also not well understood but appears to comprise other gynaecological tissue. Morphological and genetic studies have given rise to several hypotheses of aetiology, particularly for HGSOC that suggest it originates from fallopian tube epithelium. (37-39)

There are a number of theories on how precursor cells in the ovary may over time become malignant. (27) Historically until around the year 2000, the most commonly accepted hypothesis was that regular ovulation, also termed "incessant ovulation", with the associated disruption and subsequent repair of ovarian epithelium lead to acquisition of genetic damage in ovarian epithelial cells and subsequent development of ovarian cancer in susceptible individuals over time. (29) This explains why pregnancy, breast-feeding and prolonged use of the combined oral contraceptive pill can decrease a women's lifetime risk of ovarian cancer through their inhibitory impact on ovulation. (40)

Alternative hypotheses to this include:

- The gonadotropin hypothesis: circulating gonadotropins stimulate the ovarian epithelium and promote neoplastic transformation. (41)
- The hormonal hypothesis: reproductive hormones act directly on the ovarian epithelium to promote (oestrogens and androgens) or protect (progestin's) against cancer. (42)
- The inflammation hypothesis: inflammatory mediators from ovulation or co-existing disease processes damage the epithelium in the ovary and fallopian tube. (43)

In their theory on the pathogenesis of ovarian cancer Kurman and Shih proposed dividing ovarian cancers into two main groups. (44) The first of these groups, type I tumours tend to be low grade and indolent and frequently confined to the ovary at presentation. Their cell origin is from the mullerian system (cervix, endometrium and uterus) and they include low grade serous, low- grade endometrioid, clear cell, mucinous and transitional carcinomas. (45) This group shares similar cell lineage to benign cystic neoplasms and borderline tumours and importantly lacks the p53 mutation. (45) The second group of tumours, type II, account for around 75% of tumours including HGSOC, undifferentiated carcinoma and malignant mixed mesodermal tumours. Importantly p53 mutations are found in in more than 80% of cancers in keeping with their poor prognosis and diagnosis at advanced stage. (45)

In the early 2000s a further shift away from the “de novo” ovarian cancer theory came via the discovery of the serous tubal intraepithelial carcinomas (STIC) precursor lesions and that ovarian cancer itself involved the ovary as a site secondarily, with the primary lesion arising elsewhere in the pelvis. (39) The evidence around the STIC precursor theory largely involved studies of women with BRCA mutation who had had risk reduction salpingectomy and had their fallopian tubes examined in great detail. (46) Examining of the fallopian tubes in this group of women found approximately 5% harbour an early-stage intramucosal invasive tubal carcinomas, which was designated a serous tubal intraepithelial carcinomas (STIC) lesion. (46)

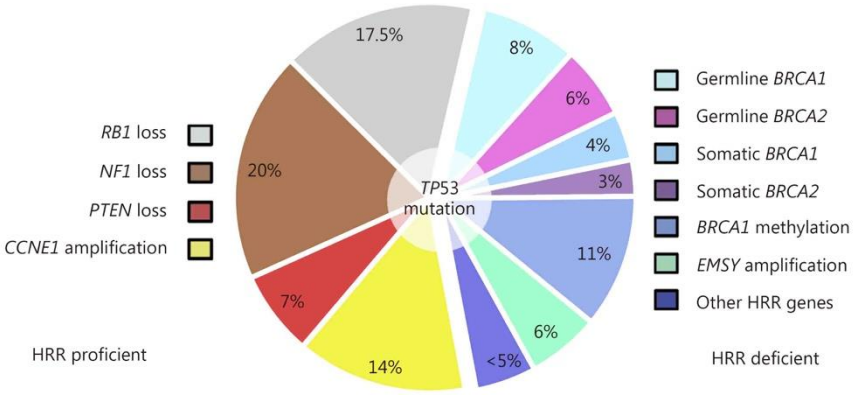
STIC is now identified as a precursor lesion for HGSOC, similar to the cervical intraepithelial neoplasia (CIN) precursors to cervical cancer. (37-39) It is though that following the development of STIC, there is a latent time window of

approximately 5 years prior to the onset of full-blown metastatic HGSC. (39)

Pre-malignant cells from a STIC may shed and implant on the ovarian surface during ovulation when the fimbriated end of the fallopian tube is in close contact with the ovary. (39) Additionally, epithelial serous pre cursor's (ESP) may shed from the fimbria by a process that is termed "pre cursor escape" and undergo malignant transformation prior to implanting on the ovary. (39) Importantly, ESPS have also been shown to contain p53 gene mutations seen in both STIC precursors and HGSOC. (39, 45)

HGSOC itself is not a single disease and has been classified into molecular subtypes on the basis of genetic changes (Figure 2). (47) A study by Tothill et al. of 285 endometroid and HGSOC cancers found a large element of heterogeneity between the different molecular subtypes of the tumours. In one of the largest study to date they performed molecular profiling on almost 300 tumours. They showed six main molecular subtypes named C1-C6. Importantly, cases of HGSOC were largely confined to 4 molecular subtypes. (47) Low grade and less aggressive tumours were confined to one subtype and those who had an earlier progression of disease were again more likely to show the reactive stroma 'C1' subtype. (47) There also appears to be a survival advantage for tumours with a high expression of immune response related genes C4. (48)

Figure 2. Molecular aberrations identified in HGSOC. (48)



From: Hollis R. L and Gourley C. Genetic and molecular changes in ovarian cancer. Cancer Biol Med. 2016 Jun;13(2):236-47

Both the recent developments in understanding the early aetiology of ovarian cancer (39, 45) and better understanding and defining heterogeneity within the HGSOC molecular subtypes, has the potential of redefining screening modalities for ovarian cancer and also the current recommendation of risk reduction salpingectomy and oophorectomy tumours in BRCA positive women (39, 45, 47, 48). The earlier diagnosis of tumour molecular subtypes may also result in chemotherapy agents being able to be targeted more effectively (see Chapter 3). (48)

1.4 Diagnosis and staging of ovarian cancer

Initial investigations for a patient with symptoms suspicious for ovarian cancer include a pelvic ultrasound scan and measurement of the serum cancer antigen-25 (CA-125) (49) to determine a Risk of Malignancy Index (RMI). The RMI combines the results of ultrasound examination, menopausal status and serum

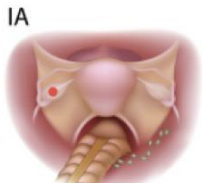
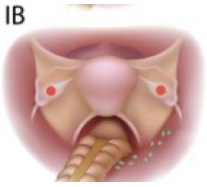
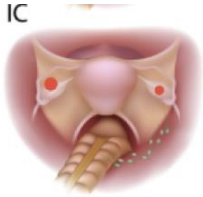
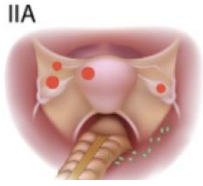
levels of cancer antigen 125 (CA-125) to provide a quantitative assessment of the risk of malignancy. A score of over 200 is predictive (sensitivity 85% and specificity 97%) for a pre-operative diagnosis of ovarian cancer. (49)

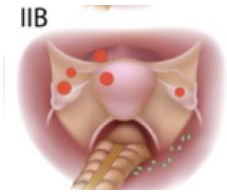
Patients with diffuse disease and abdominal ascites may have fluid aspirated for diagnostic purposes and this also allows for removal of large volume ascites and palliation of symptoms. An image guided tissue biopsy, most commonly from an omental deposit can also allow for rapid histological diagnosis in conjunction with immunohistochemical analysis to assess both the subtype and grade of the tumour. (50, 51)

Histopathology and cytology coupled with clinical and imaging features allow a confident diagnosis of the primary tumour site and provide information needed to plan treatment. As part of pre-operative planning a CT of the chest, abdomen and pelvis is frequently performed to facilitate multidisciplinary discussion and treatment planning. Staging of the tumour is not finalised until surgery is completed and specimens have been reviewed by anatomical pathologists and discussed at a meeting of the gynaecological oncology multi-disciplinary team (MDT), which is the cornerstone of management of patients with gynaecological cancers. (52) The universally accepted staging of ovarian cancer was first published in 1973 by the FIGO and revised in 1988 and again in 2014 following the improvements in knowledge of tumour origins and disease progression. (53)

In countries where appropriately trained personnel and facilities are available, standard of care for women diagnosed with ovarian cancer includes treatment in a centralised gynaecologic oncology service with input from gynaecologic oncologists and pathologists, medical oncologists and radiologists. Management of patients by a centralised multidisciplinary service has been shown to improve patient outcomes. (4, 54)

Table 1. Description and anatomic representation of FIGO staging for ovarian cancer. (55, 56)

Stage	Description	Image
I	Tumour confined to ovaries or fallopian tube(s)	
IA	Tumour limited to one ovary (capsule intact) or fallopian tube, no tumour on ovarian or fallopian tube surface, no malignant cells in the ascites or peritoneal washings	
IB	Tumour limited to both ovaries (capsules intact) or fallopian tubes No tumour on ovarian or fallopian tube surface No malignant cells in the ascites or peritoneal washings	
IC	Tumour limited to one or both ovaries or fallopian tubes, with any of the following **IC1** surgical spill intra operatively **IC2** capsule ruptures before surgery or tumour on ovarian or fallopian tube surface **IC3** malignant cells present in the ascites or peritoneal washings	
II	Tumour involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer	
IIA	Extension and/or implants on the uterus and/or fallopian tubes/and/or ovaries	

IIB	Extension to other intraperitoneal tissues	
III	Tumour involves one or both ovaries or fallopian tubes with cytologically or histologically confirmed spread outside the pelvis and metastasis to retroperitoneal lymph nodes	
IIIA	Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis **IIIA1** positive retroperitoneal LN only **IIIA1i** Metastasis </= 10mm in dimension (tumour not LN dimension) **IIIA1ii** Metastasis >10mm in greatest dimension	
IIIA2	Microscopic extrapelvic (above pelvic Abrim) peritoneal involvement with or without positive retroperitoneal nodes	
IIIB	Macroscopic peritoneal metastasis beyond the pelvic brim </= 2cm with or without positive retroperitoneal nodes. Includes extension to capsule of liver/spleen.	
IIIC	Macroscopic peritoneal metastasis beyond the pelvic brim > 2cm with or without positive retroperitoneal nodes. Includes extension to capsule of liver/spleen.	
IV	IVA pleural effusion with positive cytology	
	IVB hepatic and/or splenic parenchymal metastasis or metastasis to extra abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)	

1.5 Treatment options for advanced high-grade serous ovarian cancer of the ovary, fallopian tube or peritoneum.

Treatment for HGSOC has consisted of primary debulking surgery and adjuvant platinum and taxane-based chemotherapy as first line therapy. (4, 30) The single most important prognostic factor is the volume of residual disease (refer to Table 1) at the conclusion of primary surgery. (30) Patients with residual disease > 1cm in maximal diameter have worse survival compared to those who are optimally cytoreduced (< 1 cm) or who have no macroscopic residual disease. (57-59).

1.5.1 Primary debulking surgery (PDS)

There are several aims of PDS, including:

- Removal of large necrotic areas within tumour bulk with associated poor blood supply and concurrent poor proliferative activity, resulting in improved chemotherapy success. (60)
- Overall improvement in patient condition and immune function.
- Removing resistant clones present at the start of treatment that may cause chemotherapy failure and earlier recurrence of disease. (61, 62)

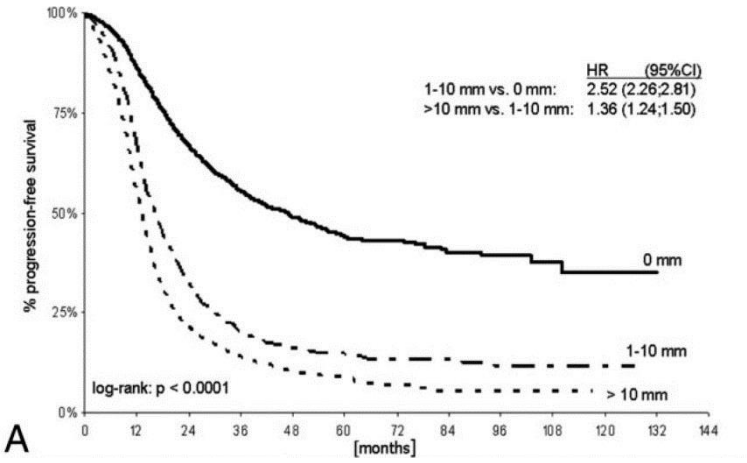
The current approach to surgery includes a hysterectomy, bilateral salpingo-oophorectomy, tumour debulking (which may involve bowel resection +/- lymphadenectomy) and omentectomy so that a woman is ideally debulked to nil macroscopic residual disease, also termed R=0. (63-66) Cytoreductive surgery is considered ‘optimal’ if the largest residual tumour after surgery is < 1cm (64). If possible, debulking to nil macroscopic residual is the goal of surgery. Internationally, surgeons report on debulking success and the sites of residual disease left at the conclusion of surgery, using the following international criteria.

Table 2. Classification of residual disease at debulking surgery for ovarian cancer. (58, 67)

Residual disease (cm)	Description
0	Debulked to nil macroscopic disease
≤ 1	The largest amount of residual disease is < 10 mm
> 1	The amount of measurable residual disease is between 10-20 mm
> 2	Bulky disease is left

Griffiths et al., (68) in 1975, were the first to report on the survival benefits in patients who were cytoreduced in surgery to less than 1.5 cm of residual disease. Since this publication, there have been many subsequent series and Cochrane meta-analyses that demonstrated improved survival benefits following optimal debulking and debulking to no residual disease. (69) This is demonstrated visually in the Kaplan Meier curve from Chi et al.'s meta-analysis of PDS for patients with bulky disease, published in 2012 (Figure 2). (6) Other factors that improve a women's overall survival in advanced ovarian cancer include (FIGO) stage at time of diagnosis, involvement of a gynaecological oncologist performing surgery, age <75, performance status and comorbidities at time of treatment. (1, 64, 66)

Figure 3. Progression-free survival by residual disease status in patients undergoing primary debulking surgery for advanced ovarian cancer. (6)



*From: Chi DS, Musa F, Dao F, Zivanovic O, Sonoda Y, Leitao MM, et al. An analysis of patients with bulky advanced stage ovarian, tubal, and peritoneal carcinoma treated with primary debulking surgery (PDS) during an identical time period as the randomized EORTC-NCIC trial of PDS vs neoadjuvant chemotherapy (NACT). Gynecologic Oncology. 2012;124(1):10-4***.**

Understandably, upfront optimal debulking to nil macroscopic disease translates into long arduous surgery and is associated with increased perioperative morbidity and mortality. The subset of women presenting with advanced stage disease who are not considered suitable candidates for PDS due to frailty and co-existing medical comorbidities, may benefit from NACT (refer to section 1.5.3).

1.5.2 The role of adjuvant chemotherapy in advanced ovarian cancer: Six cycles of carboplatin and paclitaxel - where have we come from and how did we get here?

Following optimal debulking surgery, women receive six cycles of adjuvant chemotherapy completing treatment. (70-73) For the purpose of this thesis, the key landmark trials that have shaped current chemotherapy practice in the treatment of advanced ovarian cancer (stage III and IV only) will be discussed.

Ovarian cancer has been treated with platinum-based agents (i.e. cisplatin) since the late 1970's and carboplatin-based combinations have been the standard of

care for over 15 years. (74-77) Cisplatin significantly improved the overall survival (OS) for ovarian cancer patients, leading to its adoption as the cornerstone of most chemotherapy regimens. (74-77) Since the mid-1980's, carboplatin (a cisplatin analogue) has been administered as it has a superior toxicity profile compared to cisplatin. (74-77). The next major milestone in epithelial ovarian cancer treatment was the introduction of the taxane compound paclitaxel, which in combination with cisplatin was shown to be superior to cisplatin and cyclophosphamide (GOG 111). (72, 73) Despite other drug combinations being investigated (such as in the ICON 3 trial (78), carboplatin and paclitaxel remains the 'backbone' for the treatment of advanced ovarian cancer.

Treatment can be curative (for patients with early stage disease); however, most women with HGSOC will develop recurrent disease with progressively shorter disease-free intervals, and these episodes ultimately culminate in chemoresistance. (78) The disease may be managed for more than five years for patients who had a complete pathological response after surgery and whose disease continues to respond to platinum-based drugs. (74, 79, 80)

Resistance to chemotherapy may result from a number of mechanisms including altered membrane transport, alterations in target enzymes, decreased drug activation, increased drug metabolism and inactivation, subcellular redistribution, enhanced deoxyribonucleic acid (DNA) repair, and failure of apoptosis due to mutated cell cycle proteins. (81, 82) It is unlikely that chemotherapy resistance would result from a single mechanism, and it is thought that multiple molecular mechanisms ultimately prevent the tumour from responding to the chemotherapy. (81) Even the smallest detectable cancers will eventually contain drug-resistant clones and the best chance of cure is to use two different non–cross-resistant chemotherapy regimens in alternating cycles.

Chemotherapy works by first order kinetics killing a constant fraction of cells dividing at any one time rather than a constant number of tumour cells. This means that a single dose of chemotherapy is unlikely to be curative. This 'log kill' hypothesis explains the need for intermittent courses of treatment to achieve the magnitude of cell kill to produce tumour regression. (83-85)

Dose dense weekly paclitaxel has been compared to conventional three-weekly administration in a Japanese population, which showed improved overall survival in the dose dense arm from 62 to 100 months. (86) It is important to note that ethnic differences in the expression of alleles involved in the chemotherapy drug metabolism have been reported, and when this when this study was replicated in a Caucasian population the same overall survival benefits were not demonstrated, and thus, outside of Japan, the dose dense regime is not recommended. (87)

1.5.3 NACT as an alternative to primary debulking surgery: An emerging alternative

NACT is defined as the administration of platinum-based chemotherapy prior to IDS to reduce tumour size and may be considered an alternative to primary debulking surgery (refer to section 1.8.1*)* for selected patients with HGSOC. Primary debulking surgery (PDS) carries a high risk of postoperative complications; therefore, NACT before cytoreductive surgery of women with advanced HGSOC was proposed as a means to reduce the surgical complexity in high-risk women with advanced ovarian cancer. (2)

There are several reasons to consider offering NACT as an alternative to up-front debulking surgery for HGSOC patients, these include (1):

- If the disease is suspected to be unresectable (unlikely to be successfully debulked to R0) with primary debulking surgery (i.e. if the tumour involves the porta hepatis or the small bowel mesentery)
- Patients with high perioperative risk (e.g. those who have medical co-morbidities with a poor performance status at time of diagnosis).

Treatment of HGSOC with NACT has remained controversial due to the limitations and variations in existing international research. Several studies have suggested that NACT may have superior outcomes compared to primary debulking surgery (including patients with advanced epithelial ovarian cancer) reporting that NACT was associated with achieving a higher rate of optimal cytoreduction and lower perioperative morbidity when compared to PDS. (88-90) However, opposing studies also exist and report that a lower optimal cytoreduction rate, (91-93) similar residual disease (94) and perioperative morbidity (95, 96) was present for NACT patients compared to those that had PDS.

A recent meta-analysis study further fuelled debate by reporting that NACT-IDS improved perioperative outcomes and optimal cytoreduction rates and was not inferior to PDS-CT in terms of survival outcomes. (97) The later study concluded that future research should focus on improving the efficiency of NACT.

In addition to the existing retrospective and observational studies, several randomised controlled trials (RCTs) (1, 2, 98-100) have investigated NACT and the associated outcomes for patients with advanced epithelial ovarian cancer. Two of these RCTs provided gynaecological oncologists worldwide with compelling evidence to recommend NACT to patients as an alternative non-inferior option to primary surgery with equivalent overall survival and less peri-operative morbidity and mortality. (1, 101)

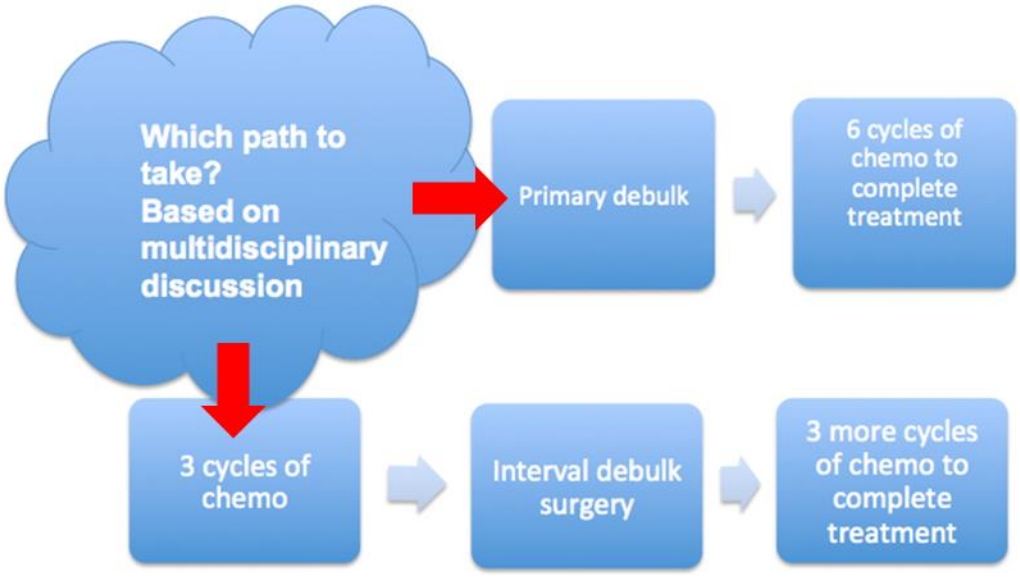
Whilst the evidence from these trials has led to an increasing trend worldwide to treat patients with NACT, (1, 101) these two trials have also received some criticism. Firstly, there was mismatched randomisation between groups and patients with bulkier disease in the NACT arms. Optimal debulking rates to R0 and R1 were much lower compared to some centres in North America, as was the resultant progression free survival and overall survival. Residual large tumour bulk at the start of chemotherapy is known to be associated with the decreased efficacy of chemotherapy and the earlier development of chemotherapy resistant clones during the course of NACT, and that may explain the lower survival rates.

Lastly, critics have highlighted the large number of recruiting centres in each trial with low caseloads. The low rates of R0 achieved called into question the level of surgical expertise at these centres. Previous authors have expressed concerns that the results of these two trials may encourage gynaecological surgeons to adopt a more conservative approach to ovarian cancer surgery and therefore may lead to deskilling of the surgical workforce. (6, 7) In an effort to address some of these concerns the TRUST trial (102) has been developed and is currently recruiting patients.

The ultimate decision on whether a patient undergoes PDS or NACT is after discussion at a gynaecological oncology MDT (see Figure 3) involving input from pathologists, radiologists, oncologists and gynaecologic oncology surgeons. The MDT takes into consideration a patient's biological age, functional status and disease distribution based on computed tomography (CT) imaging and also considers the surgeon's confidence to achieve nil macroscopic disease from either upfront primary debulking or following NACT. However, the sensitivity of CT to predict optimal cytoreduction pre-operatively is low (103) and laparoscopic

pre-staging has been suggested as an alternative to more accurately predict outcome of debulking surgery. (18) Lastly there is increasing evidence around tumour molecular testing and the biology of certain subtypes being more likely to have upper abdominal disease distribution and increased post operative morbidity. There may be a role for molecular subtype testing in planning for primary therapy in advanced HGSOC. (47, 104)

Figure 4. Current approach to treat high-grade serous ovarian cancer.



1.6 Development of the chemotherapy response score system

The use of NACT and IDS as an alternative to PDS has allowed anatomical pathologists the opportunity to assess the early tumour response of chemotherapy agents in interval debulking surgical specimens. This assessment of tumour response to NACT is both established and routinely reported on in other solid tumours including breast, (8-10) rectum, (11, 12) oesophagus, (13, 14) stomach and colon/rectum. (100, 105-107) The tumour response regression in these organs has been known to provide prognostic information and to guide post-operative adjuvant treatment planning, (8-10) and research into its prognostic role in HGSOC is greatly needed.

1.6.1 The history of the CRS in ovarian cancer

The evidence for histological tumour regression following NACT in patients with advanced ovarian cancer has been limited and conflicting. Several widely used tumour regression-grading systems have been considered for gynaecological

cancers; however, the systems used were unnecessarily complex (e.g. breast cancer tumour regression systems also included assessment of lymph nodes). Although suggested tumour grading systems for gastrointestinal tumours were relatively simple to use, the reproducibility of results remains highly variable. (108) Consequently, further investigation into a classification system specifically for HGSOC required further development and investigation.

Four observational studies investigated and assessed tumour regression after NACT in advanced-stage HGSOC and reported a correlation between the tumour response and overall survival. (17, 109-111) Unfortunately, all studies used different tumour regression scoring criteria, did not validate their criteria in independent series and did not evaluate the reproducibility of their methodologies. (17, 109-111) (refer to Table 3).

Table 3. Summary of studies that investigated tumour regression scores in response to neoadjuvant debulking surgery for advanced ovarian cancer patients.

First author	Year	Number of patients	Ovarian cancer histologic types	Predicted PFS	Predicted OS	Study limitations
Sassen S, et al. (111)	2007	49	Serous and endometrioid	No	Yes	• Small sample sizes • Observer dependence inherent to any semi quantitative evaluation • Sampling error due to tumour heterogeneity • Some patients received further palliative treatment that may have had an impact on overall survival that was not measured
Le T, et al. (17)	2007	62	Serous, mucinous, endometroids, clear cells anaplastic.	No	Yes	• Retrospective design, which has unavoidable selection bias • Unavailability of some pathologic slides for review limiting the power of our analysis
Muraji M, et al. (109)	2012	124	Serous, mucinous, endometroids, clear cells and 'other'	No	No	• Retrospective design, which has unavoidable selection bias
Petrillo M, et al. (18)	2014	322	Serous and 'others'	Yes	Yes	• Retrospective design, which has unavoidable selection bias

PFS – progression free survival, OS – overall survival.

In 2015, a study by Böhm et al. (15) described a three-tier scoring system (the Chemotherapy Response Score [CRS]) that was highly reproducible and easy for pathologists to apply in their clinical setting, regardless of experience level in gynaecological oncology pathology (see Table 4). Using a modification of the Dworak system, (12) the study demonstrated good inter-observer reproducibility and a statistically significant association with the clinical outcomes in both the test cohort (60 patients) and validation cohort (71 patients) with HGSOC stage III or IV. Furthermore, the study design identified that application of the CRS to the omental tumour deposit was superior to the application of the CRS to the primary tumour. A study published by Said et al. in 2017 further examined the CRS reproducibility. 40 samples were examined amongst 5 different groups each with three pathologists of varying ability. In this study the CRS system was found to be highly reproducible among all the pathologists' groups (K=0.761). Most notably the interobserver reproducibility was K=0.926 in those patients identified as CRS3. (112)

Table 4. The final three-tier CRS score as adopted by the ICCR in 2015. (15)

Score	Description
CRS 1	No or minimal tumour response. Mainly viable tumour with no or minimal regression-associated fibro inflammatory changes, limited to a few foci: cases in which it is difficult to decide between regression and tumour-associated desmoplasia or inflammatory cell infiltration.
CRS 2	Appreciable tumour response amid viable tumour that is readily identifiable. Tumour is regularly distributed, ranging from multifocal or diffuse regression-associated fibro inflammatory changes with viable tumour in sheets, streaks, or nodules to extensive regression-associated fibro inflammatory changes with multifocal tumour, which is easily identifiable.

CRS 3	Complete or near-complete response with no residual tumour OR minimal irregularly scattered tumour foci seen as individual cells, cell groups, or nodules up to 2 mm maximum size. Mainly regression-associated fibroinflammatory changes or, in rare cases, no or very little residual tumour in the complete absence of any inflammatory response. It is advisable to record whether there is no residual tumour or whether there is microscopic residual tumour present.

1.7 Summary

With accumulating evidence that NACT-IDS offers similar outcomes to the traditional pathway of PDS followed by chemotherapy for the subgroup (poor functional status either related to the disease or co-morbidities) of women with advanced stage HGSOC, (7) the three-tier CRS developed by Böhm provides an opportunity to reliably assess a patient's response to the chemotherapy.

The ICCR recommended that the CRS be incorporated as part of the routine pathological assessment until further studies assessing the CRS became available. Therefore, a retrospective analysis of the prognostic role of the CRS in women with advanced HGSOC undergoing neoadjuvant chemotherapy in Western Australia would help address this need.

Chapter 2:

Prognostic role of histologic tumour regression in patients receiving neoadjuvant chemotherapy for high-grade serous tubo-ovarian carcinoma[1]

[1] This is the Author's original manuscript of an article published by Coghlan E, Meniawy TM, Munro A, Bulsara M, Stewart CJ, Tan A, et al. Prognostic role of histological tumor regression in patients receiving neoadjuvant chemotherapy for high-grade serous tubo-ovarian carcinoma. *International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society*. 2017;27(4):708-13.
Available online or see p.55 of thesis.

2.1 Introduction

Ovarian cancer is a highly lethal malignancy accounting for more than 140,000 deaths annually worldwide. Most women with ovarian cancer are diagnosed with advanced stage disease, for which the standard treatment is a combination of debulking surgery and platinum-based chemotherapy.[2] Since two randomized phase 3 clinical trials demonstrated equivalent survival and reduced morbidity after neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS) compared with primary surgery,[3,4] there has been an increasing trend in many countries to treat such patients with NACT.

Histopathological tumour response to NACT is routinely assessed in breast, esophageal, and rectal cancers,[5-7] but until recently, there has not been an accepted scoring system for high-grade serous tubo-ovarian carcinoma (HGSOC), the most common histological subtype of epithelial tubo-ovarian cancer. Several studies have attempted to quantify chemo- therapy response in HGSOC and to correlate this with survival,[8-11] but their findings have been inconsistent, and none has been independently validated. Recently, Bohm et al.[12] reported a three-tier chemotherapy response score (CRS) in a test cohort of 62 HGSOC tissue specimens resected at IDS. This predicted progression-free survival (PFS) and overall survival (OS) in the test group and in a subsequent validation cohort of 71 patients. Despite calling for further studies to confirm these findings, the International Collaboration on Cancer Reporting has recently recommended the use of the CRS for the histological grading of NACT effect in HGSOC.[13]

The aim of the current study was to externally validate the prognostic role of this proposed chemotherapy response scoring system in an equivalent-sized

independent cohort of patients with advanced HGSOC treated with NACT and IDS.

2.2 Patients and methods

2.2.1 Study participants

Consecutive patients diagnosed with HGSOC between January 1, 2010, and December 31, 2014, were identified from the weekly Western Australian gynecologic oncology tumour board, a multidisciplinary meeting of the Western Australian Gynecologic Cancer Service, in which almost all patients presenting with gynecological cancer in the state are reviewed. Patients were eligible if they had histologically and/or cytologically confirmed stages IIIC and IV ovarian, fallopian tube, or primary peritoneal high-grade serous carcinoma - hereafter collectively referred to as HGSOC - treated by NACT and IDS. Because the CRS system requires a histological assessment of tumour response specifically within the omentum, patients who were classified as stage IIIC according to earlier (pre-2014) FIGO criteria with metastatic disease confined to the lymph nodes were excluded from the study (see the ‘‘Pathology Review’’ section). Follow-up data were available up to the study census date, November 23, 2016. Laboratory and clinical data including patient age, FIGO stage, chemotherapy regimen, the surgeon’s visual assessment of completeness of the IDS (macroscopic residual disease classified as zero residual, >1 or <1 cm), and serum CA-125 at baseline and before IDS were obtained from the patient’s medical records. Germline BRCA mutation status was ascertained from the state-wide Genetic Services Western Australia, where available. Neoadjuvant chemotherapy was routinely administered as an initial combination of intravenous carboplatin (AUC 5Y6) and paclitaxel (either q3 weekly, 175 mg/m^2, or q1 weekly, 80 mg/m^2). Interval debulking surgery was performed by midline laparotomy in all cases and included

total extrafascial hysterectomy, bilateral salpingo oophorectomy, and infracolic omentectomy as a minimum.

Study data were obtained after ethical approval from the St John of God Subiaco Hospital Human Research Ethics Committee (reference no. 806) and The University of Notre Dame Australia (Fremantle) Human Research Ethics Committee (reference no. 016106F).

2.2.2 Pathology review

Slides obtained from formalin-fixed paraffin-embedded tissue blocks were reviewed by one of three gynecological pathologists (A.T., C.J.R.S., M.H.E.K.), who assigned a CRS independently to any given in the original histopathology reports. Tumour regression scores were then assigned based on the omental sample showing the least NACT response according to the proposed CRS, as summarized as follows. In general, a CRS of 1 and a CRS of 3 equated to greater than 95% and less than 5% tumour viability, respectively[13]:

- *Chemotherapy response score of 1.* No or minimal tumour response. Mainly viable tumour with no or minimal tumour regression - associated fibroinflammatory changes, limited to a few foci: cases in which it is difficult to decide between regression and tumour-associated desmoplasia or inflammatory cell infiltration.
- *Chemotherapy response score of 2.* Appreciable tumour response amid viable tumour that is readily identifiable. Tumour is regularly distributed, ranging from multifocal or diffuse regression-associated fibroinflammatory changes with viable tumour in sheets, streaks, or nodules to extensive regression-associated fibroinflammatory changes with easily identifiable multifocal residual tumour.

- *Chemotherapy response score of 3*. Complete or near complete response with no residual tumour or minimal irregularly scattered tumour foci seen as individual cells, cell groups, or nodules of up to 2-mm maximum size. Mainly regression-associated fibroinflammatory changes or, in rare cases, no or very little residual tumour in the complete absence of any inflammatory response.

Consensus scoring was achieved after review and discussion in a minority of cases where there was initial difficulty separating a CRS of 1 from a CRS of 2, or a CRS of 2 from a CRS of 3.

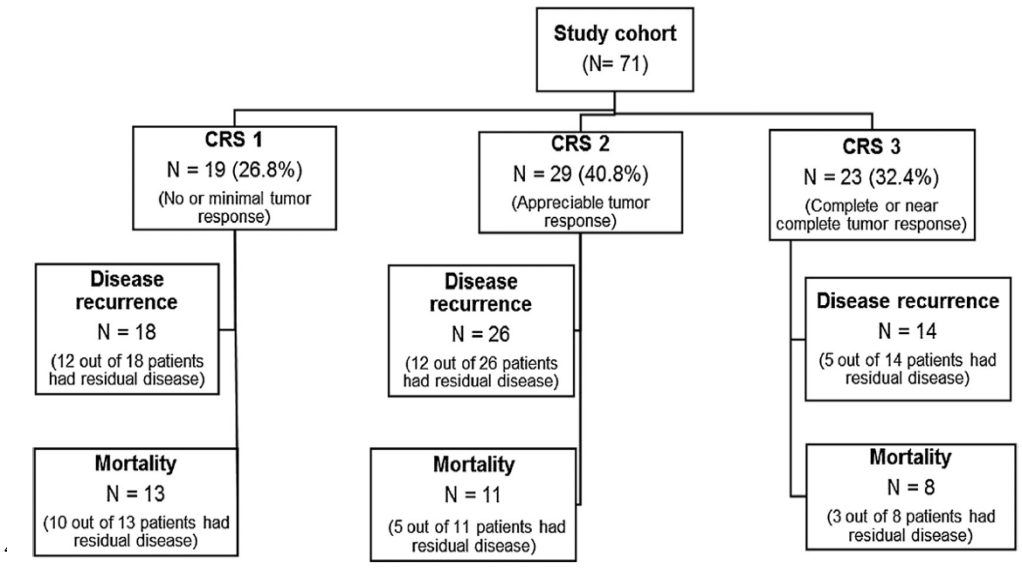
2.3 Statistics

Statistical analysis was performed using the statistical software program Stata 13.0 (Stata Statistical Software Release 13; Stata Corp LP, College Station, TX). Fisher exact test was used to examine group differences between CRS, PFS, and OS. Time-to-event analysis was performed using Cox models to investigate patient and clinical factors associated with PFS and OS in univariate and multivariate models. Progression-free survival was defined as the time from the commencement of NACT to disease recurrence or death (whichever was the earliest) or to the date of the last follow-up for patients who had not recurred before the study census date. Overall survival was defined as the time from the commencement of NACT to death. Variables included in the model were age at diagnosis (years), the stage of disease, the surgeon's visual assessment of completeness of the IDS (macroscopic residual disease), and the CRS. Statistical significance was determined as a P value less than 0.05, and the 95% confidence intervals (CIs) for hazard rate ratios were calculated. Plausible interaction terms were tested using likelihood ratio tests. Violation of the Cox model proportional hazard assumption was tested using Schoenfeld residuals.

2.4 Results

Of 620 patients diagnosed with tubo-ovarian cancer between January 1, 2010, and December 31, 2014, 93 patients (15%) were treated by NACT. Patients were excluded if metastatic disease was confined to the lymph nodes (n = 2), tumour histology was not high-grade serous carcinoma (n = 15), or there was no omental disease (n = 5). Seventy-one patients were eligible for analysis. Fifty-one patients (71.8%) had radiological stage IIIC disease, and 20 (28.2%) had stage IV disease. Of the 71 patients, 45 (63.5%) completed 3 cycles of NACT before interval surgery. Eleven patients (15.5%) received 4 cycles, 10 (14%) had more than 4 cycles, and 5 (7%) completed less than 3 cycles before IDS (Supplementary Table 10). Interval surgery was scheduled approximately 21 days after the last NACT cycle. Of the 71 patients in the study cohort, 19, 29, and 23 patients had CRSs of 1, 2, and 3, respectively. An overview of the study cohort is presented in Figure 5. Patient characteristics, details of NACT regimen, and clinicopathological findings are shown in Table 5. Median age at diagnosis was 67 years (range, 31.3 to 85 years). At the census date of November 23, 2016, 58 (82%) patients had recurred and 32 (45%) had died of any cause (Fig. 4).

Figure 5. Overview of the study cohort.



The results of the univariate and multivariate analyses for PFS are summarized in Table 6. Univariate analysis indicated that patients with a CRS of 1 (CRS of 1 vs CRS of 3; hazard ratio [HR], 3.77; 95% CI, 1.83-7.78; P = 0.000) and any macroscopic residual disease as visualized by the surgeon at the completion of interval debulking (any disease vs R0; HR, 1.99; 95% CI, 1.17-3.38; P = 0.011) were at an increased risk of progression. Patients with a CRS of 1 had a significantly shorter PFS compared with those with a CRS of 3 (median PFS, 11 vs 26 months). In a multivariate model, the CRS retained significance for PFS (CRS of 1 vs CRS of 3; HR, 3.13; 95% CI, 1.43-6.87; P = 0.004).

A Kaplan-Meier graph (Fig. 5) was constructed reporting OS by CRS (censoring women at the time of death or last known follow-up date). More than 50% of the patients with a CRS of 1 were deceased by 24 months compared with 16% of patients with a CRS of 3.

Table 5. Patient baseline characteristics, histologic scoring of tissue and surgical outcomes at surgical interval debulking.

Characteristic	Study cohort (N=71)	Percentage (%)
Median age in years (range)	67 (31.3 – 85)	
Neoadjuvant chemotherapy regimen		
q1 weekly	53	74.6
q3 weekly	18	25.4
Outcome of interval debulking surgery *(residual disease)*		
Zero residual (R0)	39	54.9
≤1cm	26	36.6
> 1 cm	6	8.5
CRS Score		
CRS 1	19	26.8
CRS 2	29	40.8
CRS 3	23	32.4
Disease distribution*		
Lower abdominal	27	38
Upper abdominal	44	62
Total cycles of chemotherapy (neoadjuvant + adjuvant) administered		
≤ 6	51	84.5
> 6	20	15.5
Did chemotherapy regimen change post interval debulking surgery?		
No	60	84.5
Yes	11	15.5
CA-125 overall percentage decrease		
< 86	19	26.8
≥ 86	49	69.0
Unknown	3	4.2
Germline BRCA mutation status		
BRCA1	4	5.6
BRCA2	1	1.4
Inconclusive	17	24.0
Unknown	45	63.4
Patient declined testing	3	4.2
Did not qualify for testing	1	1.4

Table 6. Univariate and multivariate survival analysis of prognostic factors for progression free survival.

	Univariate analysis			Multivariate analysis		
Factors	**Hazard ratio**	**95% Confidence Interval**	***p***	**Hazard ratio**	**95% Confidence Interval**	***p***
CRS						
Score 1	3.77	1.83 – 7.78	0.000	3.13	1.43 – 6.87	0.004
Score 2	1.85	0.96 – 3.55	0.064	1.71	0.88 – 3.36	0.116
Score 3	1.00	-	-	1.00	–	-
Age at diagnosis	1.00	0.98 – 1.03	0.874	1.00	0.97 – 1.02	0.619
FIGO stage						
IIIC	1.00	-	-	1.00	-	-
IV	0.88	0.49 – 1.57	0.657	0.70	0.37 – 1.34	0.286
Residual disease at IDS						
R0	1.00	-	-	1.00	-	-
Any disease present	1.99	1.17 – 3.38	0.011	1.60	0.88 – 2.91	0.120

CRS; Chemotherapy Response Score; FIGO, International Federation of Gynaecology and Obstetrics; IDS, Interval debulking surgery.

Figure 6. Estimation of PFS according to pathological evaluation (CRS 1, 2 or 3) for patients who received NACT.

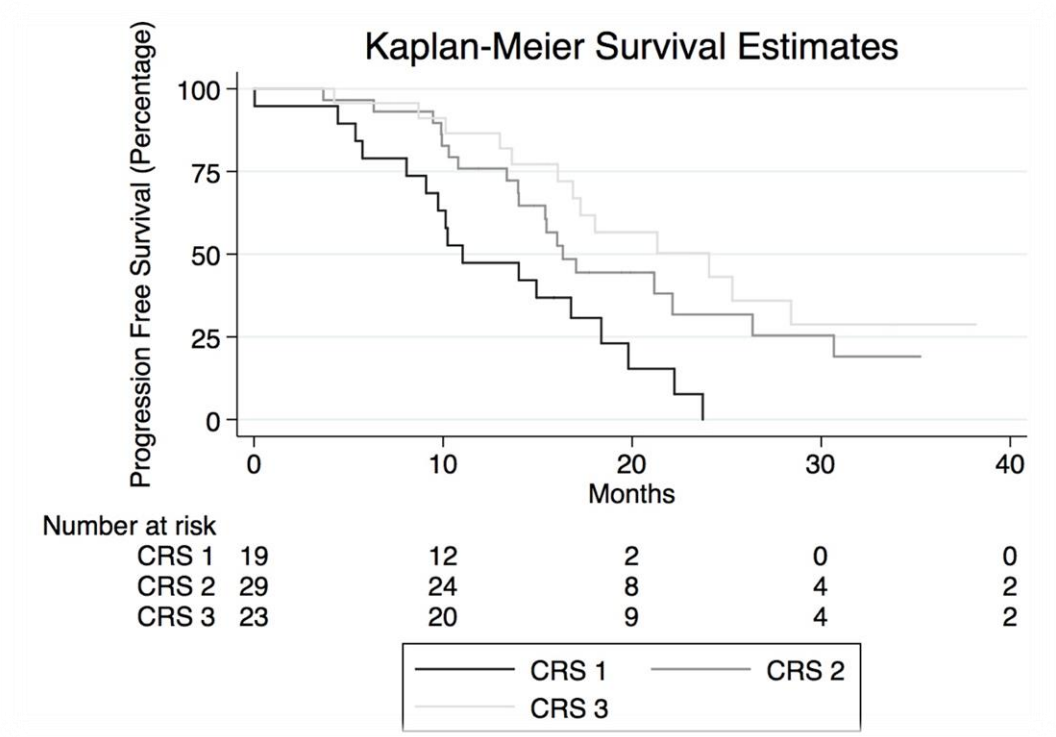
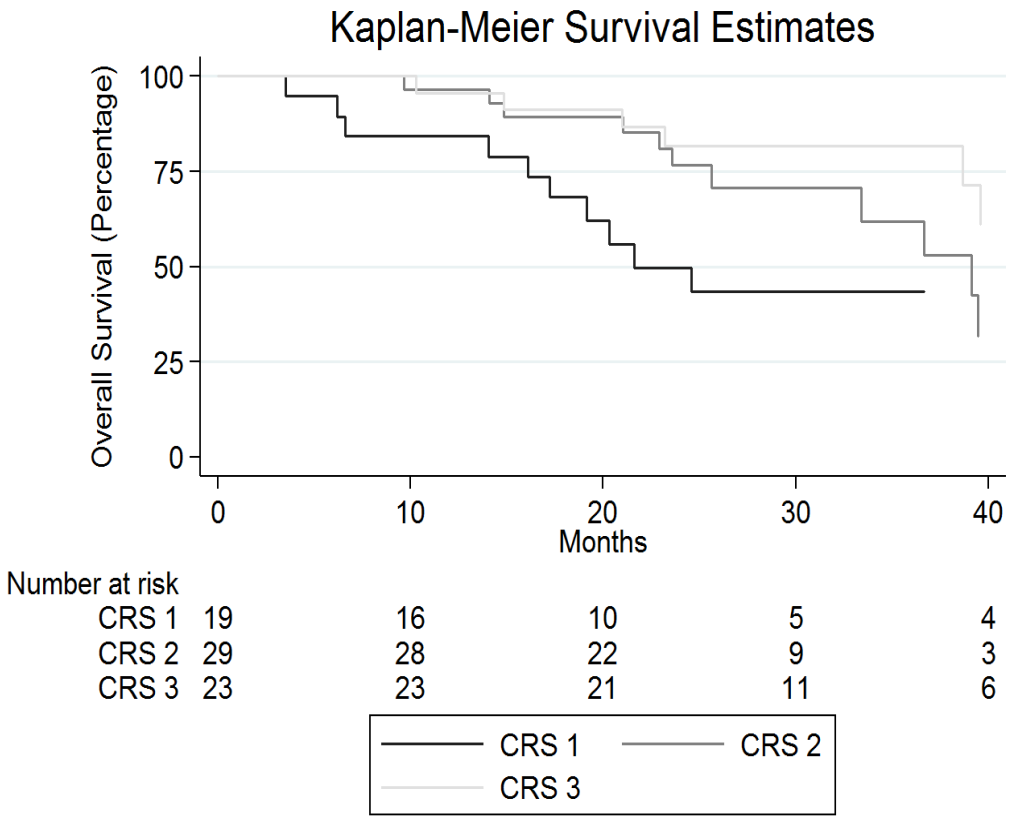


Table 7. Univariate and multivariate survival analysis of prognostic factors for overall survival.

	Univariate analysis			Multivariate analysis		
Factors	**Hazard ratio**	**95% CI**	***p***	**Hazard ratio**	**95% CI**	***p***
CRS						
Score 1	2.81	1.16 – 6.79	0.022	2.39	0.47 – 3.08	0.079
Score 2	1.41	0.56 – 3.52	0.462	1.21	0.90 – 6.30	0.695
Score 3	1.00	-	-	1.00	-	-
Age at diagnosis	1.02	0.98 – 1.06	0.293	1.03	0.98 – 1.08	0.198
FIGO stage						
IIIC	1.00	-	-	1.00	-	-
IV	1.45	0.71 – 2.96	0.306	1.89	0.86 – 4.15	0.110
Residual disease at IDS						
R0	1.00	-	-	1.00	-	-
Any disease present	1.91	0.94- 3.89	0.073	1.31	0.60 – 2.89	0.497

CRS, Chemotherapy Response Score; FIGO, International Federation of Gynecology and Obstetrics; IDS, Interval debulking surgery.

Figure 7. Estimation of OS according to pathological evaluation (CRS 1, 2 or 3) for patients who received NACT.



As per Bohm et al., a multivariate survival analysis of prognostic factors for PFS combining CRSs of 1 and 2 versus CRS of 3 is shown in Table 8 and the corresponding Kaplan-Meier graph in Supplementary Figure 5. Patients with CRSs of 1 and 2 combined were twice as likely to progress during the study period compared with patients with a CRS of 3 (HR, 2.0; 95% CI, 1.06-3.78; P = 0.032; median PFS, 16 vs 26 months). The CRS was not significant for OS (CRSs of 1 and 2 vs 3; HR, 1.57; 95% CI, 0.68-3.65; P = 0.291) (Table 10 and Supplementary Figure 7). The results of the univariate and multivariate analyses for OS are summarized in Table 7.

Complete CA-125 data were available for 68 patients (95.8%). Median pre-treatment levels were 773.5 kU/L (range, 81-34,000 kU/L). Sixty-three patients (88.7%) had a reduction of 50% or greater, and 41 (60.3%) had a reduction 90% or greater from baseline to pre-IDS levels. CA-125 reduction did not correlate with the CRS (P = 0.751) (Table 10). Germline BRCA mutation status was also investigated, but most of the patients (63.4%) had not undergone testing, and therefore, this variable was not included in the statistical analysis.

In additional multivariate analyses including the year of entry (categorized as 2009-2012 and 2013-2014), the chemo- therapy regimen (weekly vs three-weekly paclitaxel), and the number of NACT cycles before IDS, there was no significant association between these variables and PFS or OS (Supplementary Tables 8-12).

2.5 Discussion

To our knowledge, this is the first external study to validate the CRS described by Bohm et al., which has been proposed by the International Collaboration on Cancer Reporting for use in reporting HGSOC after NACT and IDS.[13]. In our study, the CRS (CRSs of 1 and 2 vs CRS of 3) strongly predicted PFS and OS

on univariate analysis, consistent with the findings of Bohm et al. The CRS retained prognostic significance for PFS on multivariate analysis when the HRs were adjusted for age, disease stage, and macroscopic residual disease as visualized by the surgeon at the completion of interval debulking. On multivariate analysis, the CRS was not significant for OS and this is also consistent with the findings of Bohm et al.

Data from previous studies that have investigated the prognostic role of histological tumour response to NACT in epithelial tubo-ovarian cancer are conflicting. In a retrospective cohort of 58 patients who were free of macroscopic residual disease after IDS, tumour response did not reliably predict survival.[8] In contrast, a recent retrospective analysis of 57 epithelial ovarian cancer patients demonstrated that complete pathological response (defined as no residual microscopic tumour in the surgical resection specimens) was associated with PFS but not with OS.[14]. In another study of 124 patients treated by NACT, lack of any measurable tumour regression in the histopathology specimens of 11 patients was associated with worse OS. It is difficult to draw meaningful conclusions from the findings of these studies because of heterogeneity in the criteria used to classify tumour regression, histological ovarian cancer subtypes included in their cohorts, and duration of follow-up.

After treatment with NACT, complete resection of all macroscopic disease at interval surgery has been shown to be the strongest independent variable in predicting OS in 2 randomized phase 3 clinical trials.[3,4] In the present study, macroscopic residual disease at surgery was significantly associated with worse PFS on univariate analysis but did not retain significance on multivariate analysis. There was a nonsignificant trend to worse OS for any macroscopic residual disease on univariate analysis.

Our study has several limitations including the selection bias inherent in its retrospective design, small sample size, and the relatively short median follow-

up. Germline and somatic BRCA mutations are associated with improved PFS and OS,[15-18] and it is a limitation of our study that it was not possible to ascertain mutation status for over 60% of the cohort because mutation testing was not part of routine care in Western Australia until 2013.

The CRS has been shown to have a high interobserver reproducibility, especially in identifying the subgroup of patients with the best chemotherapy response,[19] but its prognostic relevance based on the current findings is uncertain. The CRS may be used as an intermediate end point in clinical trials because it can be measured earlier than disease progression and OS and might also be used to stratify patients for clinical trials, possibly including changes in chemotherapy for apparent nonresponders, post-IDS. The role of the CRS in predicting survival in patients with HGSOC treated by NACT requires prospective validation in an unselected cohort, ideally as part of a randomized controlled trial of NACT versus primary debulking surgery, such as the EORTC 55971 TRUST trial, which has recently started recruiting.[20] The present study is the first to validate the CRS proposed by Bohm et al., but further studies that incorporate additional biomarkers of response and prognosis are required. In conclusion, the CRS may predict survival in patients with HGSOC after NACT, but until its prognostic value has been proven, caution should be exercised before this scoring system is incorporated into routine practice.

2.6 Supplementary data tables

Table 8. Supplementary multivariate survival analysis of prognostic factors for progression free survival for time with chemotherapy as a categorical variable.

		Multivariate analysis (N= 71)	
Factors	**Hazard ratio**	**95% Confidence Interval**	***p***
CRS Score			
Score 1	1.68	0.75 – 3.91	0.225
Score 2	1.04	0.48 – 2.34	0.925
Score 3	1.00	-	-
Age at diagnosis	1.00	0.28 – 1.21	0.873
Time to chemotherapy (days)			
< 28	1.00	-	-
≥ 28	0.86	0.42 – 1.75	0.678
Chemotherapy regimen			
q1 weekly	1.00	-	-
q3 weekly	1.00	0.47 – 2.12	0.995
FIGO stage			
IIIC	1.00	-	-
IV	0.63	0.28 – 1.41	0.266
Disease distribution			
Lower abdominal	1.00	-	-
Upper abdominal	2.17	1.11 – 4.21	0.023
Residual disease at IDS			
R0	1.00	-	-
Any disease present	1.96	0.97 – 3.98	0.061
Overall percentage difference in CA-125 score			
< 86 %	1.00	-	-
≥ 86 %	0.58	0.28 – 1.21	0.148

CA, Cancer Antigen; CRS, Chemotherapy Response Score; FIGO, International Federation of Gynecology and Obstetrics; IDS, Interval debulking surgery

Table 9. Supplementary multivariate survival analysis of prognostic factors.

		Multivariate analysis (N= 71)	
Factors	**Hazard ratio**	**95% Confidence Interval**	***p***
CRS Score			
Score 1	1.81	0.45 – 7.28	0.403
Score 2	0.97	0.25 – 3.85	0.968
Score 3	1.00	-	-
Age at diagnosis	1.03	0.97 – 1.09	0.369
Time to chemotherapy (days)			
< 28	1.00	-	-
≥ 28	1.31	0.38 – 4.54	0.669
Chemotherapy regimen			
q1 weekly	1.00	-	-
q3 weekly	1.68	0.53 – 5.34	0.377
FIGO stage			
IIIC	1.00	-	-
IV	1.47	0.49 – 4.39	0.493
Disease distribution			
Lower abdominal	1.00	-	-
Upper abdominal	2.29	0.80 – 6.55	0.124
Residual disease at IDS			
R0	1.00	-	-
Any disease present	3.58	1.14 – 11.22	0.029
Overall percentage difference in CA-125 score			
< 86 %	1.00	-	-
≥ 86 %	0.46	0.16 – 1.33	0.152

CA, Cancer Antigen; CRS, Chemotherapy Response Score; FIGO, International Federation of Gynecology and Obstetrics; IDS, Interval debulking surgery.

Table 10. Fischer's exact test investigating if CA-125 reduction clinically correlated to CRS.

	CA-125 (N = 68)		
CRS	< 86%	≥ 86 %	**Total**
Score 1	7	11	18
Score 2	6	22	28
Score 3	6	16	22
Total	19	49	81

** Fisher's exact test = 0.751

Table 11. Fischer's exact test investigating if a change in chemotherapy regimen was clinically correlated to CRS and progression free survival.

	Progression status		
Chemotherapy changed status	**No progression**	**Progressed**	**Total**
Yes	1	7	8
No	1	10	11
Total	2	17	19

** Fisher's exact test = 1.00

Table 12. Fischer's exact test investigating if a change in chemotherapy regimen was clinically correlated to CRS and overall survival.

	Survival status		
Chemotherapy changed status	**Alive**	**Died**	**Total**
Yes	2	6	8
No	6	5	11
Total	8	11	19

** Fisher's exact test = 0.352

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Coghlan E, Munro A, Bulsara M, Magee D, Stewart JR C, Tang A, Koay E, Cohen P. Prognostic role of histologic tumor regression in patients receiving neoadjuvant chemotherapy for high-grade serous ovarian carcinoma. *Int J Gynecol Cancer* 2017;27(4):708-713 (doi: 10.1097/IGC.0000000000000945.).

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Prognostic Role of Histological Tumor Regression in Patients Receiving Neoadjuvant Chemotherapy for High-Grade Serous Tubo-ovarian Carcinoma

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Objective: Our objective was to validate the prognostic role of the chemotherapy response score (CRS), which has been proposed for measuring tumor response to neoadjuvant chemotherapy in patients with high-grade serous tubo-ovarian carcinoma, in predicting progression-free survival (PFS) and overall survival (OS).

Methods: A retrospective cohort study was conducted of patients with advanced high-grade serous tubo-ovarian carcinoma diagnosed between January 1, 2010, and December 31, 2014, and treated with neoadjuvant chemotherapy. Treatment-related tumor regression was determined according to the 3-tier CRS, and results were compared with standard clinicopathological variables. Survival analysis was performed using Cox proportional hazards models and the log-rank test.

Results: Seventy-one patients were eligible for analysis. Median OS was 25.5 months. Fifty-eight patients (82%) had disease recurrence and 32 (45%) had died at study census. Of the 71 patients, 19, 29, and 23 patients had a CRS of 1, 2, and 3, respectively. On univariate analysis, the CRS significantly predicted PFS (hazard ratio [HR], 3.77; 95% confidence interval [CI], 1.83–7.78; $P = 0.000$) and OS (HR, 2.81; 95% CI, 1.16–6.79; $P = 0.022$). In a multivariate model, the CRS was significantly associated with PFS (HR, 2.81; 95% CI, 1.16–6.79; $P = 0.022$) but not with OS (HR, 2.39; 95% CI, 0.47–3.08; $P = 0.079$). Patients with CRS of 1 and 2 combined were twice as likely to progress during the study period compared with patients with a CRS of 3 (HR, 2.0; 95% CI, 1.06–3.78; $P = 0.032$; median PFS, 16 vs 26 months). No significant association was observed for OS (CRS 1/2 vs 3; HR, 1.57; 95% CI, 0.68–3.65; $P = 0.291$).

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Conclusions: In this study, the CRS showed independent prognostic significance for PFS but not for OS.

Key Words: High-grade serous carcinoma, Neoadjuvant chemotherapy, Chemotherapy response score validation, Ovarian cancer, Prognosis

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Ovarian cancer is a highly lethal malignancy accounting for more than 140,000 deaths annually worldwide.[1] Most women with ovarian cancer are diagnosed with advanced stage disease, for which the standard treatment is a combination of debulking surgery and platinum-based chemotherapy.[2] Since 2 randomized phase 3 clinical trials demonstrated equivalent survival and reduced morbidity after neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS) compared with primary surgery,[3,4] there has been an increasing trend in many countries to treat such patients with NACT.

Histopathological tumor response to NACT is routinely assessed in breast, esophageal, and rectal cancers,[5–7] but until recently, there has not been an accepted scoring system for high-grade serous tubo-ovarian carcinoma (HGSOC), the most common histological subtype of epithelial tubo-ovarian cancer. Several studies have attempted to quantify chemotherapy response in HGSOC and to correlate this with survival,[8–11] but their findings have been inconsistent and none has been independently validated. Recently, Bohm et al[12] reported a 3-tier chemotherapy response score (CRS) in a test cohort of 62 HGSOC tissue specimens resected at IDS. This predicted progression-free survival (PFS) and overall survival (OS) in the test group and in a subsequent validation cohort of 71 patients. Despite calling for further studies to confirm these findings, the International Collaboration on Cancer Reporting has recently recommended the use of the CRS for the histological grading of NACT effect in HGSOC.[13]

The aim of the current study was to externally validate the prognostic role of this proposed chemotherapy response scoring system in an equivalent-sized independent cohort of patients with advanced HGSOC treated with NACT and IDS.

PATIENTS AND METHODS

Study Participants

Consecutive patients diagnosed with HGSOC between January 1, 2010, and December 31, 2014, were identified from the weekly Western Australian gynecologic oncology tumor board, a multidisciplinary meeting of the Western Australian Gynecologic Cancer Service, in which almost all patients presenting with gynecological cancer in the state are reviewed. Patients were eligible if they had histologically and/or cytologically confirmed stages IIIC and IV ovarian, fallopian tube, or primary peritoneal high-grade serous carcinoma—hereafter collectively referred to as HGSOC—treated by NACT and IDS. Because the CRS system requires a histological assessment of tumor response specifically within the omentum, patients who were classified as stage IIIC according to earlier (pre-2014) International Federation of Gynecology and Obstetrics (FIGO) criteria with metastatic disease confined to the lymph nodes were excluded from the study (see the "Pathology Review" section). Follow-up data were available up to the study census date, November 23, 2016. Laboratory and clinical data including patient age, FIGO stage, chemotherapy regimen, the surgeon's visual assessment of completeness of the IDS (macroscopic residual disease classified as zero residual, ≤1 or >1 cm), and serum CA-125 at baseline and before IDS were obtained from the patient's medical records. Germline *BRCA* mutation status was ascertained from the statewide Genetic Services Western Australia, where available. Neoadjuvant chemotherapy was routinely administered as an initial combination of intravenous carboplatin (AUC 5–6) and paclitaxel (either q3 weekly, 175 mg/m^2, or q1 weekly, 80 mg/m^2). Interval debulking surgery was performed by midline laparotomy in all cases and included total extrafascial hysterectomy, bilateral salpingooophorectomy, and infracolic omentectomy as a minimum.

Study data were obtained after ethical approval from the St John of God Subiaco Hospital Human Research Ethics Committee (reference no. 806) and The University of Notre Dame Australia (Fremantle) Human Research Ethics Committee (reference no. 016106F).

Pathology Review

Slides obtained from formalin-fixed paraffin-embedded tissue blocks were reviewed by 1 of 3 gynecological pathologists (A.T., C.J.R.S., M.H.E.K.) who assigned a CRS independently to any given in the original histopathology reports. Tumor regression scores were then assigned based on the omental sample, showing the least NACT response according to the proposed CRS as summarized as follows. In general, a CRS of 1 and a CRS of 3 equated to greater than 95% and less than 5% tumor viability, respectively[13]:

- *Chemotherapy response score of 1.* No or minimal tumor response. Mainly viable tumor with no or minimal tumor regression–associated fibroinflammatory changes, limited to a few foci; cases in which it is difficult to decide between regression and tumor-associated desmoplasia or inflammatory cell infiltration.

- *Chemotherapy response score of 2.* Appreciable tumor response amid viable tumor that is readily identifiable. Tumor is regularly distributed, ranging from multifocal or diffuse regression–associated fibroinflammatory changes with viable tumor in sheets, streaks, or nodules to extensive regression–associated fibroinflammatory changes with easily identifiable multifocal residual tumor.
- *Chemotherapy response score of 3.* Complete or near complete response with no residual tumor or minimal irregularly scattered tumor foci seen as individual cells, cell groups, or nodules of up to 2-mm maximum size. Mainly regression-associated fibroinflammatory changes or, in rare cases, no or very little residual tumor in the complete absence of any inflammatory response.

Consensus scoring was achieved after review and discussion in a minority of cases where there was initial difficulty separating a CRS of 1 from a CRS of 2, or a CRS of 2 from a CRS of 3.

Statistics

Statistical analysis was performed using the statistical software program Stata 13.0 (Stata Statistical Software Release 13; StataCorp LP, College Station, TX). Fisher exact test was used to examine group differences between CRS, PFS, and OS. Time-to-event analysis was performed using Cox models to investigate patient and clinical factors associated with PFS and OS in univariate and multivariate models. Progression-free survival was defined as the time from the commencement of NACT to disease recurrence or death (whichever was the earliest) or to the date of the last follow-up for patients who had not recurred before the study census date. Overall survival was defined as the time from the commencement of NACT to death. Variables included in the model were age at diagnosis (years), the stage of disease, the surgeon's visual assessment of completeness of the IDS (macroscopic residual disease), and the CRS. Statistical significance was determined as a P value less than 0.05, and the 95% confidence intervals (CIs) for hazard rate ratios were calculated. Plausible interaction terms were tested using likelihood ratio tests. Violation of the Cox model proportional hazard assumption was tested using Schoenfeld residuals.

RESULTS

Of 620 patients diagnosed with tubo-ovarian cancer between January 1, 2010, and December 31, 2014, 93 patients (15%) were treated by NACT. Patients were excluded if metastatic disease was confined to the lymph nodes (n = 2), tumor histology was not high-grade serous carcinoma (n = 15), or there was no omental disease (n = 5). Seventy-one patients were eligible for analysis. Fifty-one patients (71.8%) had radiological stage IIIC disease, and 20 (28.2%) had stage IV disease. Of the 71 patients, 45 (63.5%) completed 3 cycles of NACT before interval surgery. Eleven patients (15.5%) received 4 cycles, 10 (14%) had more than 4 cycles, and 5 (7%) completed less than 3 cycles before IDS (Supplementary Table 10, http://links.lww.com/IGC/A452). Interval surgery was scheduled approximately 21 days after the last NACT cycle. Of the 71 patients in the study cohort, 19, 29, and 23 patients had CRSs of 1, 2, and 3, respectively. An overview of the study cohort is presented in Figure 1. Patient characteristics, details of NACT regimen, and clinicopathological findings are shown in Table 1. Median age at diagnosis was 67 years (range, 31.3–85 years). At the census date of November 23, 2016, 58 (82%) patients had recurred and 32 (45%) had died of any cause (Fig. 1).

The results of the univariate and multivariate analyses for PFS are summarized in Table 2. Univariate analysis indicated that patients with a CRS of 1 (CRS of 1 vs CRS of 3; hazard ratio [HR], 3.77; 95% CI, 1.83–7.78; $P = 0.000$) and any macroscopic residual disease as visualized by the surgeon at the completion of interval debulking (any disease vs R0; HR, 1.99; 95% CI, 1.17–3.38; $P = 0.011$) were at an increased

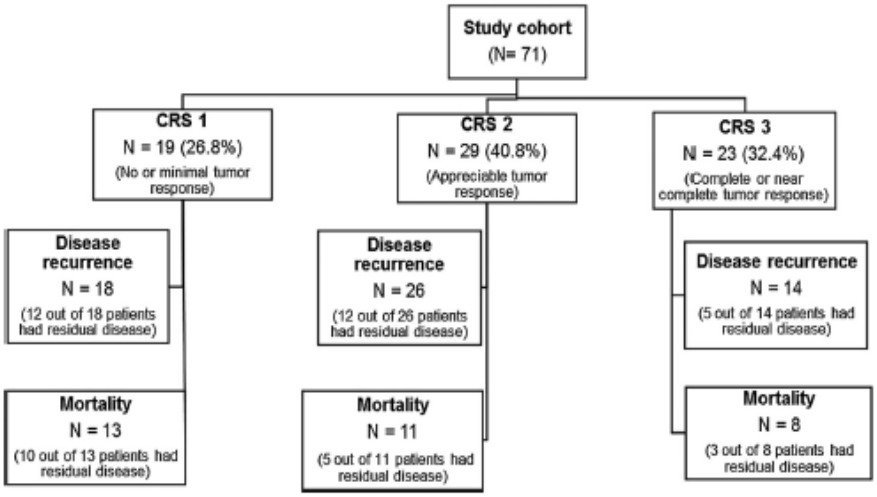

FIGURE 1. Overview of the study cohort.

TABLE 1. Patient baseline characteristics, histological scoring of tissue, and surgical outcomes at surgical interval debulking

Characteristic	Study Cohort (N = 71)	Percentage, %
NACT regimen		
q1 weekly	53	74.6
q3 weekly	18	25.4
Outcome of IDS, residual disease		
Zero residual, R0	39	54.9
≤1 cm	26	36.6
>1 cm	6	8.5
CRS		
CRS of 1	19	26.8
CRS of 2	29	40.8
CRS of 3	23	32.4
Disease distribution		
Lower abdomen	27	38.0
Upper abdomen	44	62.0
Total cycles of chemotherapy (neoadjuvant + adjuvant) administered		
≤6	51	84.5
>6	20	15.5
Did chemotherapy regimen change post-IDS?		
No	60	84.5
Yes	11	15.5
CA-125 overall percentage decrease		
<86	19	26.8
≥86	49	69.0
Unknown	3	4.2
Germline *BRCA* mutation status		
BRCA1	4	5.6
BRCA2	1	1.4
Inconclusive	17	24.0
Unknown	45	63.4
Patient declined testing	3	4.2
Did not qualify for testing	1	1.4

risk of progression. Patients with a CRS of 1 had a significantly shorter PFS compared with those with a CRS of 3 (median PFS, 11 vs 26 months) (Fig. 2). In a multivariate model, the CRS retained significance for PFS (CRS of 1 vs CRS of 3; HR, 3.13; 95% CI, 1.43–6.87; $P = 0.004$).

A Kaplan-Meier graph (Fig. 3) was constructed reporting OS by CRS (censoring women at the time of death or last known follow-up date). More than 50% of the patients with a CRS of 1 were deceased by 24 months compared with 16% of patients with a CRS of 3.

As per Bohm et al, a multivariate survival analysis of prognostic factors for PFS combining CRSs of 1 and 2 versus CRS of 3 is shown in Supplementary Table 1 (http://links.lww.com/IGC/A452) and the corresponding Kaplan-Meier graph in Supplementary Figure 1 (http://links.lww.com/IGC/A453). Patients with CRSs of 1 and 2 combined were twice as likely to progress during the study period compared with patients with a CRS of 3 (HR, 2.0; 95% CI, 1.06–3.78; $P = 0.032$; median PFS, 16 vs 26 months). The CRS was not significant for OS (CRSs of 1 and 2 vs 3; HR, 1.57; 95% CI, 0.68–3.65; $P = 0.291$) (Supplementary Table 2, http://links.lww.com/IGC/A452 and Supplementary Figure 2, http://links.lww.com/IGC/A453). The results of the univariate and multivariate analyses for OS are summarized in Table 3.

TABLE 2. Univariate and multivariate survival analysis of prognostic factors for PFS

	Univariate Analysis			Multivariate Analysis		
Factors	HR	95% CI	*P*	HR	95% CI	*P*
CRS						
Score 1	3.77	1.83–7.78	0.000	3.13	1.43–6.87	0.004
Score 2	1.85	0.96–3.55	0.064	1.71	0.88–3.36	0.116
Score 3	1.00	—	—	1.00	—	—
Age at diagnosis	1.00	0.98–1.03	0.874	1.00	0.97–1.02	0.619
FIGO stage						
IIIC	1.00	—	—	1.00	—	—
IV	0.88	0.49–1.57	0.657	0.70	0.37–1.34	0.286
Residual disease at IDS						
R0	1.00	—	—	1.00	—	—
Any disease present	1.99	1.17–3.38	0.011	1.60	0.88–2.91	0.120

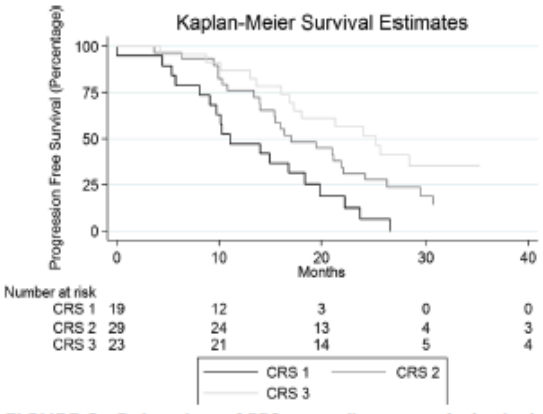

FIGURE 2. Estimation of PFS according to pathological evaluation (CRS of 1, 2, or 3) for patients who received NACT.

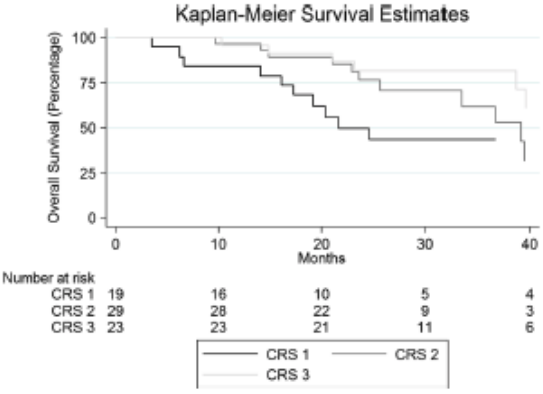

FIGURE 3. Estimation of OS according to pathological evaluation (CRS of 1, 2, or 3) for patients who received NACT.

Complete CA-125 data were available for 68 patients (95.8%). Median pretreatment levels were 773.5 kU/L (range, 81–34,000 kU/L). Sixty-three patients (88.7%) had a reduction of 50% or greater, and 41 (60.3%) had a reduction 90% or greater from baseline to pre-IDS levels. CA-125 reduction did not correlate with the CRS ($P = 0.751$) (Supplementary Table 3, http://links.lww.com/IGC/A452). Germline *BRCA* mutation status was also investigated, but most of the patients (63.4%) had not undergone testing, and therefore, this variable was not included in the statistical analysis.

In additional multivariate analyses including the year of entry (categorized as 2009–2012 and 2013–2014), the chemotherapy regimen (weekly vs three-weekly paclitaxel), and the number of NACT cycles before IDS, there was no significant association between these variables and PFS or OS (Supplementary Tables 4–10, http://links.lww.com/IGC/A452).

DISCUSSION

To our knowledge, this is the first external study to validate the CRS described by Bohm et al, which has been proposed by the International Collaboration on Cancer Reporting for use in reporting HGSOC after NACT and IDS.[13] In our study, the CRS (CRSs of 1 and 2 vs CRS of 3) strongly predicted PFS and OS on univariate analysis, consistent with the findings of Bohm et al. The CRS retained prognostic significance for PFS on multivariate analysis when the HRs were adjusted for age, disease stage, and macroscopic residual disease as visualized by the surgeon at the completion of interval debulking. On multivariate analysis, the CRS was not significant for OS and this is also consistent with the findings of Bohm et al.

Data from previous studies that have investigated the prognostic role of histological tumor response to NACT in epithelial tubo-ovarian cancer are conflicting. In a retrospective cohort of 58 patients who were free of macroscopic residual disease after IDS, tumor response did not reliably predict survival.[8] In contrast, a recent retrospective analysis of 57 epithelial ovarian cancer patients demonstrated that complete pathological response (defined as no residual microscopic tumor in the surgical resection specimens) was associated with PFS but not with OS.[14] In another study of 124 patients treated by NACT, lack of any measurable tumor regression in the histopathology specimens of 11 patients was associated with worse OS.[9] It is difficult to draw meaningful conclusions from the findings of these studies because of heterogeneity in the criteria used to classify tumor regression, histological ovarian cancer subtypes included in their cohorts, and duration of follow-up.

After treatment with NACT, complete resection of all macroscopic disease at interval surgery has been shown to be the strongest independent variable in predicting OS in 2 randomized phase 3 clinical trials.[3,4] In the present study, macroscopic residual disease at surgery was significantly associated with worse PFS on univariate analysis but did not retain significance on multivariate analysis. There was a nonsignificant trend to worse OS for any macroscopic residual disease on univariate analysis.

Our study has several limitations including the selection bias inherent in its retrospective design, small sample size, and the relatively short median follow-up. Germline and somatic *BRCA* mutations are associated with improved PFS and OS,[15–18] and it is a limitation of our study that it was not possible to ascertain mutation status for over 60% of the cohort because mutation testing was not part of routine care in Western Australia until 2013.

The CRS has been shown to have a high interobserver reproducibility, especially in identifying the subgroup of patients with the best chemotherapy response,[19] but its prognostic relevance based on the current findings is uncertain. The CRS may be used as an intermediate end point in

TABLE 3. Univariate and multivariate survival analysis of prognostic factors for OS

	Univariate Analysis			Multivariate Analysis		
Factors	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
CRS						
Score 1	2.81	1.16–6.79	0.022	2.39	0.47–3.08	0.079
Score 2	1.41	0.56–3.52	0.462	1.21	0.90–6.30	0.695
Score 3	1.00	—	—	1.00	—	—
Age at diagnosis	1.02	0.98–1.06	0.293	1.03	0.98–1.08	0.198
FIGO stage						
IIIC	1.00	—	—	1.00	—	—
IV	1.45	0.71–2.96	0.306	1.89	0.86–4.15	0.110
Residual disease at IDS						
R0	1.00	—	—	1.00	—	—
Any disease present	1.91	0.94–3.89	0.073	1.31	0.60–2.89	0.497

clinical trials because it can be measured earlier than disease progression and OS and might also be used to stratify patients for clinical trials, possibly including changes in chemotherapy for apparent nonresponders, post-IDS. The role of the CRS in predicting survival in patients with HGSOC treated by NACT requires prospective validation in an unselected cohort, ideally as part of a randomized controlled trial of NACT versus primary debulking surgery, such as the EORTC 55971 TRUST trial, which has recently started recruiting.[20] The present study is the first to validate the CRS proposed by Bohm et al, but further studies that incorporate additional biomarkers of response and prognosis are required. In conclusion, the CRS may predict survival in patients with HGSOC after NACT, but until its prognostic value has been proven, caution should be exercised before this scoring system is incorporated into routine practice.

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Chapter 3:

Discussion

3.1 Introduction

The main purpose of this thesis was to test the hypothesis that the CRS score was associated with the survival outcomes in patients with advanced HGSOC undergoing NACT-IDS. This study successfully met its first objective by externally validating the three-tier CRS developed by Bohm et al. (15) The three anatomical pathologists who participated in this study showed ease and reproducibility of assigning a CRS to our Western Australian study of 71 women.

Similarly, this study also found that outcomes for both PFS and OS were in keeping with the original paper by Bohm et al. and addressed the second objective of the thesis, which was to determine the prognostic significance of the CRS score in advanced ovarian cancer.

Since the publication of the paper there have been three further groups publish on both the reproducibility of the CRS as well as its prognostic significance for progression free survival and overall survival. (113-115) Singh et al., in a slightly larger cohort of 100 Indian patients showed that CRS did not correlate to PFS in multivariate modelling when adjusting for debulking status with CRS 1+2 having 16 months PFS vs CRS 3 18 months PFS. However, these varying results could be explained by less than 25% of the patients in their study group being optimally debulked compared with over 50% in our group and 45% in the original Bohm et al. paper. Optimal debulking and residual disease post-surgery is considered the most important factor affecting progression free and overall survival.

The second publication since our paper by Lee et al. involved 110 Korean women and showed that CRS was significant for PFS in CRS 1+2 compared with CRS 3 being 14.5 and 18.6 months respectively. (114) However, only one third of

the patients in this cohort had six total cycles of chemotherapy, compared with 85% of the patients in our study having six total cycles of chemotherapy in keeping with current recommended international practice.

A third group from the Dana Faber Cancer Centre in Boston have recently published an analysis of the CRS in 68 patients and consistent with the findings of the previous studies, found that a CRS of 1 or 2 was associated with a shorter median progression-free survival (10.9 months; 95% confidence interval, 9-14) compared to a CRS of 3 (18.9 months; 95% CI, 18-24; P=0.020).

Drawing on these data from Canada and the United Kingdom, Australia, India, Korea and the United States, these five papers have demonstrated that the CRS is a reproducible and prognostic tool for women with advanced HGSOC undergoing NACT-IDS.

3.2 Implications of research findings

The three-tier CRS classification system based on histopathological examination has been recently proposed for HGSOC to assess response to NACT by the International Collaboration on Cancer Reporting. (19) Universal adoption of CRS may have the following implications for clinical practice:

- Be utilised as a predictor of PFS and OS for patients that are selected for NACT and IDS.
- Be utilised as an endpoint for clinical trials investigating novel chemotherapy, immunotherapy and targeted agents. (116)
- Act as a biomarker for NACT response in women with advanced disease and may allow for rapid assessment of drug efficiency in clinical trials.
- Provide additional information to support the counselling of patients that need to determine continuation of chemotherapy or to cease curative

treatment and seek palliative care services to ensure quality of life is maximised in final stages of life.

- Be implemented into guidelines for ‘best practice’ to manage women diagnosed with HGOSC who are treated by NACT.

3.3 Strengths and limitations

A major strength of this study is that it was based on all patients diagnosed with HGSOC from a stable and isolated Western Australia population. The benefits of this include:

- Almost complete case ascertainment;
- Minimal loss to follow-up;
- Findings are applicable to the wider Australian setting; and
- Pathology review conducted by experts in the area.

The study does, however, also have some limitations, which include the selection bias that is inherent in its retrospective design and the relatively short median follow-up. As with all retrospective studies, the data utilised has a number of constraints. Examples may include, the quality of the data (e.g. data completeness), confounding variables that may not be present in the dataset (e.g. lifestyle factor or other existing comorbidities), and lack of other relevant clinical details (i.e. a patient’s choice to cease treatment). Extending the duration of follow-up time would increase the study’s power to perform multivariate models controlled for confounders (i.e. stage of disease, residual disease and patient age of diagnosis).

The first patients that were included into this study and underwent IDS, were prior to the landmark papers of Vergote et al. (2) and CHORUS. (1) In these earlier years IDS would have been chosen as the best treatment option for these

patients as they would have been deemed to not be ideal surgical candidates, thus there would also be the factors of the patient's poor functional status and medical comorbidities.

Germline and somatic BRCA mutation status is also associated with improved PFS and OS; however, it was not possible to ascertain BRCA status for over 60% of the cohort in this thesis as referral for mutation testing was not part of routine care in Western Australia until 2013, and it is possible that this may have biased the results.

3.4 Future avenues for research

Worldwide the management of women with HGSOC remains challenging due to the disease being diagnosed at a late stage in the majority of cases. The following research is now being undertaken to further explore the clinical significance and role of the CRS for patients diagnosed with HGSOC and are well suited to NACT with IDS:

- An international multicentre patient level meta-analysis that stratifies patients into CRS categories to further the prognostic validation of PFS and OS.
- Correlating CRS categories with HGSOC molecular subtypes; for example, one might hypothesise that patients with a CRS3 (complete or near complete pathological response to NACT) would enrich for germline or somatic BRCA mutations or other defects in the homologous DNA repair pathway.
- The importance of the CRS and its role in predicting patients with platinum resistant disease: implications to enhance their management and molecular modelling/biomarkers to extend/improve survival outcomes for these patients.

- The CRS may be used as an endpoint in clinical trials as a surrogate for survival. Indeed, a Western Australian led phase II study, “iPRIME” (ACTRN1261800010920) will investigate two immunotherapy agents, Durvalumab and Tremelimumab, in combination with standard NACT in newly diagnosed women with advanced HGSOC and the trial’s primary endpoint is the CRS.

The CRS appears to be a surrogate marker for progression-free survival in women with advanced HGSOC treated by NACT and may also be used as an endpoint in clinical trials to allow for rapid assessment of therapeutic efficacy. This may also have the potential to expedite both the development and approval of differing treatments for patients with early stage disease, which currently occurs in patients with breast cancer. (117)

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Appendix 1: Statement of Contribution of Others

Paul Cohen	Primary supervisor for research undertaken by Dr Coghlan. Development and review of study design, data analysis, statistical analysis, multiple iterations of manuscript and assistance in developing conference presentations.
Aime Powell and Jim Codde	Co-supervisors for research undertaken by Dr Coghlan. Review of study design, data analysis, statistical analysis, multiple iterations of manuscript and conference presentations.
Adeline Tan, Colin Stewart and Eleanor Koay	Expert gynaecologic oncology pathologists who undertook a comprehensive specimen slide review and assigned the CRS scores. Reviewed scientific manuscript for publication.
Cassie Nichols	Provided expert advice regarding Genetic Services of WA data variables (i.e. BRCA mutation) and facilitated approved access to these data. Reviewed scientific manuscript for publication.
Dan Magee	Assisted in data collection and cleaning of raw data. Reviewed scientific manuscript for publication.
Jason Tan, Raj Mohan, Stuart Salfinger and Yee Leung	Western Australian Gynaecological Oncologists who provided access to patient level data in both public and private sectors. Provided clinical advice and acumen as required. Reviewed scientific manuscript for publication.
Max Bulsara	Professor of Biostatistics who verified and approved all statistical analyses. Provided expert statistical advice throughout the research project to ensure the results were comprehensive and robust.
Tarek Meniway	Expert medical oncologist who provided assistance in developing data variables, specifically relating to neoadjuvant and adjuvant chemotherapy. Additionally, completed a comprehensive manuscript review.

Appendix 2: Human Research Ethics Approvals

ST JOHN OF GOD
Subiaco Hospital

8 June 2016

Dr Paul Cohen
c/o WOMEN Centre
20/2 McCourt Street
WEST LEEDERVILLE WA 6007

Dear Dr Cohen,

Re: The Prognostic Role of Histopathological Tumour Response to Neoadjuvant Chemotherapy in High Grade Serous Ovarian Carcinoma *(Our ref No: 806)*

Thank you for keeping the St John of God Health Care (SJGHC) Human Research Ethics Committee ("the Committee") updated on the progress of the above study.

I advise that the Committee at its meeting on 8 June 2016, approved the following:

1. Addition of Edwina Coghlan as an Investigator

as per your letter dated 13 May 2016.

Please find attached signed and dated Committee membership list.

Yours sincerely

Clinical Professor Dr Simon Dimmitt
Chairman,
St John of God Health Care Human Research Ethics Committee

cc. Sanela Bilic, Project Manager, Gynaecological Cancer Research Group, SJGSH

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19 Mouat St (PO Box 1225) Fremantle WA 6959
+61 8 9433 0555 | enquiries@nd.edu.au

21 June 2016

Dr Paul Cohen & Dr Edwina Coghlan
Women Centre
Suite 20
2 McCourt St
West Leederville WA 6007

Dear Paul and Edwina,

Reference Number: 016106F

Project title: "The prognostic role of histopathological tumour response to neoadjuvant chemotherapy in high grade serous ovarian carcinoma."

Thank you for submitting the above project for review. It is noted that you have ethics approval for this project from St John of God Health Care HREC, reference number 904. Your application has been assessed as qualifying for a Cross-Institutional approval and is therefore exempt from HREC review. I am pleased to advise that ethical clearance has been granted for this proposed study.

Other UNDA students and researchers identified as working on this project are:

Name	School	Role
Dr Aime Munro	School of Health Sciences	Co-Investigator

All research projects are approved subject to standard conditions of approval. Please read the attached document for details of these conditions.

Should you have any queries about this project, please contact me at #2964 or Natalie.Giles@nd.edu.au.

Yours sincerely,

Dr Natalie Giles
Research Ethics Officer
Research Office

cc: Dr Raoul Oehmen, Acting SRC Chair, School of Medicine

Appendix 3: The Cancer Detection Centre for Women Research Scholarship

THE UNIVERSITY OF NOTRE DAME AUSTRALIA

30 May 2016

Dr Edwina Coghlan
2/3 Princes Street
COTTESLOE WA 6011

Dear Edwina

RE: OFFER OF SCHOLARSHIP AND TERMS OF OFFER

I am very pleased to inform you that you have been offered ***The Cancer Detection Centre for Women Research Scholarship*** at The University of Notre Dame Australia, Fremantle.

The Scholarship is valued at $7,500 per annum for the duration of your studies. The Scholarship will be paid in two instalments of $3,750 per year, until Semester 2, 2017 included, providing your Satisfactory Academic Progress has been confirmed by the School of Medicine.

To accept the terms of the Scholarship, please read and sign the *Acceptance of Scholarship* and *Gift Expenditure Form* enclosed and return by **Tuesday 7 June 2016.**

Should you have any questions, please do not hesitate to contact me (08) 9433 0692 or email Stefania.Demurtas@nd.edu.au.

Congratulations and I wish you all the best with your studies this year.

Yours sincerely

Ms Stefania Demurtas
Senior Development Officer, Office of University Relations

Appendix 4: Poster delivered at the International Gynecological Cancer Society Meeting

Prognostic factors including histologic tumor regression in patients receiving neoadjuvant chemotherapy for high-grade serous ovarian carcinoma

Edwina Coghlan[1,2]; Tarek M. Meniawy[1,3,12]; Aime Munro[1,2]; Max Bulsara[2]; Colin JR Stewart[1,4]; Adeline Tan[5,9]; M H Eleanor Koay[6]; Daniel MaGee[7]; Jim Codde[2]; Jason Tan[1,4,7,8]; Stuart G. Salfinger[1,4,7]; Ganendra R. Mohan[1,4]; Yee Leung[4]; Andrew Dean[1]; Martin Buck[1]; Cassandra B. Nichols[10,11]; Paola Chivers[2]; Melanie J. McCoy[1,3]; Paul A. Cohen[1,2,4,8].

PURPOSE

A histopathologic scoring system, the chemotherapy response score (CRS), has been proposed recently for measuring tumor response to neoadjuvant chemotherapy (NACT) in patients with high grade serous ovarian carcinoma (HGSOC). Our aim was to validate the prognostic role of the CRS in predicting progression free survival (PFS) and overall survival (OS) in HGSOC.

PATIENTS AND METHODS

A retrospective cohort study of patients with advanced stage HGSOC diagnosed between 1 January 2010 - 31 December 2014 and treated with NACT. Treatment-related tumor regression was determined according to the three-tier CRS and the results compared with standard clinicopathological variables. Survival analysis was performed using Cox proportional hazard models and the log-rank test.

RESULTS

A total of 71 patients were treated with NACT. Median overall survival (OS) was 20.3 months. Forty-nine (69%) patients had disease recurrence and 22 (31%) had died at survival census. Of 71 patients, 19, 29 and 23 patients had a CRS of 1, 2 and 3 respectively. Residual disease, disease distribution and CRS significantly predicted PFS and OS on univariate analysis. In a multivariate model, only residual disease (hazard ratio (HR), 3.23; 95% CI, 1.10 – 9.48; p = .033) was significantly associated with OS. CRS was not an independent prognostic factor for OS on multivariate analysis (HR, 1.75; 95% CI, 0.48 – 6.39; p = 0.396).

CONCLUSION

In this study, absence of residual disease after IDS was associated with longer overall survival. The CRS did not have independent prognostic significance.

TABLE 1: Overview of study cohort

	Study Cohort (N = 71)		
	CRS 1	CRS 2	CRS 3
Total	N = 19 (26.8%) No/Minimal tumour response	N = 29 (40.8%) Appreciable tumour response	N = 23 (32.4%) Complete/near complete tumour response
Disease recurrence	N = 17 (89.5%) 11 out of 17 patients had residual disease	N = 19 (65.5%) 10 out of 19 patients had residual disease	N = 13 (56.5%) 3 out of 13 patients had residual disease
Mortality	N = 11 (57.9%) 8 out of 11 patients had residual disease	N = 7 (24.1%) 5 out of 7 patients had residual disease	N = 4 (17.4%) 2 out of 4 patients had residual disease

TABLE 2: Patient baseline characteristics, histologic scoring of tissue and surgical outcomes at surgical interval debulking

Characteristic	Study cohort (N = 71)	%
Neoadjuvant chemotherapy regimen		
q1 weekly	53	74.6
q3 weekly	18	25.4
Outcome of IDS (residual disease)		
Zero residual (R0)	39	54.9
≤ 1cm	26	36.6
> 1cm	6	8.5
CRS		
CRS 1	19	26.8
CRS 2	29	40.8
CRS 3	23	32.4
Disease distribution		
Lower abdominal	27	38.0
Upper abdominal	44	62.0
Did chemotherapy regimen change post IDS?		
No	60	84.5
Yes	11	15.5
CA-125 overall percentage decrease		
< 86%	19	26.8
≥ 86%	49	69.0
Unknown	3	4.2
Germline BRCA mutation status		
BRCA1	4	5.6
BRCA2	1	1.4
Inconclusive	17	24.0
Unknown	45	63.4
Patient declined testing	3	4.2
Did not qualify for testing	1	1.4

FIGURE 1: Estimation of overall survival according to pathological evaluation (CRS) for patients who received NACT followed by IDS

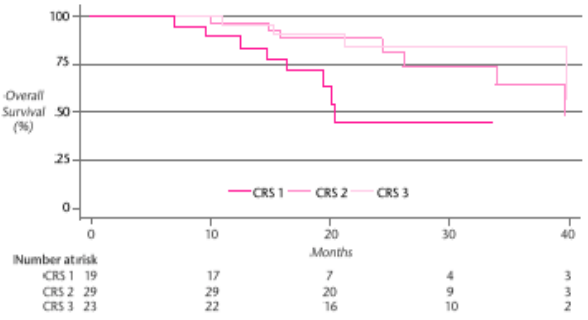

TABLE 3: Univariate and multivariate survival analysis of prognostic factors for overall survival

	Univariate analysis			Multivariate analysis		
Factors	Hazard radio	95% Confidence Interval	p	Hazard radio	95% Confidence Interval	p
CRS						
Score 1	4.04	1.27 - 12.88	0.018	1.75	0.48 – 6.39	0.396
Score 2	1.46	0.43 - 5.00	0.544	0.99	0.26 – 3.39	0.987
Score 3	1.00	-	-	1.00	–	-
Age at diagnosis	1.03	0.98 – 1.07	0.238	1.02	0.97 – 1.09	0.370
Chemotherapy regimen						
q1 weekly	1.00	-	-	1.00	–	-
q3 weekly	2.10	0.90 - 4.95	0.087	1.59	0.52 – 4.86	0.416
FIGO stage						
IIIC	1.00	-	-	1.00	–	-
IV	1.15	0.48 – 2.76	0.750	1.43	0.49 - 4.18	0.509
Disease distribution						
Lower abdominal	1.00	-	-	1.00	–	-
Upper abdominal	2.72	1.16 - 6.37	0.021	2.20	0.77 – 6.26	0.139
Residual disease at IDS						
R0	1.00	-	-	1.00	–	-
Disease present	3.37	1.30 - 8.79	0.013	3.23	1.10 - 9.48	0.033
% difference in CA-125 score						
< 86%	1.00	-	-	1.00	–	-
≥ 86%	0.37	0.16 - 0.88	0.025	0.46	0.16 – 1.31	0.146

AUTHOR AFFILIATIONS
St John of God Hospital Bendat Family Comprehensive Cancer Centre Subiaco, Western Australia; Harry Perkins Institute of Medical Research, University of Notre Dame Australia, Western Australia; School of Medicine and Pharmacology, University of Western Australia, Western Australia; School of Women's and Infants' Health, University of Western Australia, Western Australia; School of Surgery, University of Western Australia, Western Australia; Department of Histopathology, King Edward Memorial Hospital, Western Australia; School of Medicine, University of Notre Dame Australia, Western Australia; NHMRC Clinical Trials Centre, Western Australia; St John of God Pathology, St John of God Subiaco Hospital, Western Australia