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Dosimetry, clinical factors and medication intake influencing urinary symptoms after prostate radiotherapy: an analysis of data from the RADAR prostate radiotherapy trial

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CONFLICTS OF INTEREST NOTIFICATION

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ABSTRACT

Purpose/Objective: To identify dosimetry, clinical factors and medication intake impacting urinary symptoms after prostate radiotherapy.

Material and Methods: Data describing clinical factors and bladder dosimetry (reduced with principal component (PC) analysis) for 754 patients treated with external beam radiotherapy accrued by TROG 03.04 RADAR prostate radiotherapy trial were available for analysis. Urinary symptoms (frequency, incontinence, dysuria and haematuria) were prospectively assessed using LENT-SOMA to a median of 72 months. The endpoints assessed were prevalence (grade $\geq$ 1) at the end of radiotherapy (representing acute symptoms), at 18-, 36- and 54-month follow-ups (representing late symptoms) and peak late incidence including only grade $\geq$ 2. Impact of factors were assessed using multivariate logistic regression models with correction for over-optimism.

Results: Baseline symptoms, non-insulin dependent diabetes mellitus, age and PC1 (correlated to the mean dose) impact symptoms at >1 timepoints. Associations at a single timepoint were found for cerebrovascular condition, ECOG status and non-steroidal anti-inflammatory drug intake. Peak incidence analysis shows the impact of baseline, bowel and cerebrovascular condition and smoking status.

Conclusions: The prevalence and incidence analysis provide a complementary view for urinary symptom prediction. Sustained impacts across time points were found for several factors while some associations were not repeated at different time points suggesting poorer or transient impact.

INTRODUCTION

Advances in prostate radiotherapy aimed at reducing complications call for accurate understanding of the relationship between clinical factors and the resultant complications. Urinary symptoms following external beam radiotherapy (EBRT) are gaining more importance as they affect more patients than rectal symptoms, especially with dose escalation, despite the use of more conformal treatment techniques [1]. There is currently a lack of rigorous evidence regarding urinary complications [2].

Apart from the dosimetric factors [3-6], urinary symptoms have been demonstrated to be influenced by other comorbidities, including hypertension [7, 8], diabetes [9, 10] and baseline urinary symptoms [11, 12]. There are suggestions that the intake of certain medications related has an impact on the interaction between radiation treatment and biological systems, which influences the expression of symptoms [10, 13]. Anti-hypertensive medication [5] and anti-coagulants [10] were associated with a higher risk of acute and late urinary symptoms, respectively. The protective impact of angiotensin converting enzyme (ACE)-inhibitor (ACE) intake has been suggested in other organ systems [13].

Considerable clinical and medication intake data were collected in the TROG-03.04 trial of Randomised Androgen Deprivation and Radiotherapy (RADAR-NCT00193856) [14, 15]. In this analysis, we sought to identify the dosimetric and clinical factors, including medication intake, impacting urinary symptoms after prostate radiotherapy.

METHODS AND MATERIALS

Patients and treatments

The RADAR trial examined the influence of the duration of androgen suppression (AS) therapy with or without bisphosphonate treatment, adjuvant with radiotherapy. Data collection, protocol requirements and QA have been summarised previously [15-18]. Accrual was from 23 centres in Australia and New Zealand between 2003 and 2008. All participants received centre-nominated radiotherapy where 813 had EBRT (without a brachytherapy boost) to either 66, 70 or 74 Gy delivered in up to 2 treatment phases. Of these, 754 had sufficient dosimetric and clinical data available for inclusion in the analysis presented here, comprising;

- Digital treatment plan export consisting of axial computed tomography (CT) slices at maximum 5 mm spacing.
- Form-based information on patient clinical factors comprising physical characteristics, comorbidities, medication intake and lifestyle factors captured at randomisation.

More complete descriptions of the study protocol and treatment technique specifications can be found elsewhere [18].

Principal components of bladder dose-surface histogram

The digital radiotherapy treatment plan for every patient, incorporating CT images, delineated anatomical structures, treatment plan parameters and 3-dimensional dose matrix, was independently reviewed using the SWAN [19] and archived. Delineation of the bladder was not mandatory for RADAR, thus, all plans were manually reviewed and bladder outlining either verified or manually added. No specific dose constraints were applied by RADAR for the bladder. Dose-surface histograms (DSH) of the bladder wall were calculated independently using SWAN to ensure consistency across datasets submitted from different centres [20].

Physical doses to each voxel in the dose matrix for each treatment phase were combined to generate EQD2 – the equivalent dose in 2 Gy fractions - using an α/β of 6 Gy [2, 21]. Dose bins of 0.1 Gy were used to calculate the dose received by the bladder wall surface using relative surface area of tissue receiving more than a threshold dose. Due to the high correlation between dose-area indices (Appendix-A), the use of such data in a multivariate analysis would result in multicollinearity problems. Thus, the DSH indices in multiples of 5 Gy were used to produce uncorrelated principal components which account for most of the variances in smaller dimensions. Applications of this dimensional reduction method has been shown in previous dose-response studies [22, 23].

Symptom prevalence and incidence

Urinary symptoms (dysuria, incontinence, frequency and haematuria) were assessed using LENT-SOMA [24]. Baseline were assessed at randomisation prior to any intervention. The patients were then followed up in clinic every 3 months for 18 months, then 6 monthly up to 5 years post randomisation and then annually. The median follow-up of 72 months is available. Schmid *et al.* demonstrates that the majority of urinary symptoms following EBRT are transient [25]. Reporting the incidence rate alone may overestimate the actual symptom burden and may have higher level of cumulative noise [25, 26], thus, both prevalence and incidence are reported in the current analysis. The symptom prevalence at the end of radiotherapy treatment represents the acute symptoms while the prevalence at 18-, 36- and 54-month post randomisation follow-ups represent the late symptoms. Grade ≥ 1 are taken into account and not dichotomised to maximise data utilisation. Potential noise associated with low-grade symptoms is kept at a minimal level in the prevalence analysis as it is not accumulated across follow-up. Peak symptom grade at or beyond the 12-month follow-up (~5 month post-radiotherapy) was utilised in the incidence analysis. Grade ≥ 2 at any time as long as the follow-up is available is considered as an ‘event’. For the rest of this paper, dysuria after the end of treatment will be abbreviated as Dys_{acute} while at 18-, 36- and 54-month post randomisation, and the peak event as Dys_{18} , Dys_{36} , Dys_{54} and Dys_{Peak} , respectively. Similar convention is used for haematuria (Haem), incontinence (Incont) and frequency (Freq). Follow-up data were frozen at November 2012.

Statistical analysis

The potential predictors include the reduced dosimetric variables (based on principal component analysis) and all clinical factors listed in Table 1. Logistic (for incidence) and ordinal logistic (for prevalence) regression methods were used to create logit prediction models for the associations between potential predictors and endpoints, first, by univariate analysis. Collinearity among the variables was assessed using correlation coefficients. When two or more variables are correlated (Spearman correlation coefficient, $\rho > .5$), only one variable which has been previously suggested to be associated to urinary symptoms was included in the multivariate variable selection. Clinical variables whose distributions are too narrow (i.e. prevalence $< 5\%$) were not included. Backward variable selection where the deletion or inclusion of variable is based on Bayesian information criterion (BIC) was performed to identify the main variables that explain the endpoints. BIC introduces a penalty term for the number of parameters in the model and the procedure stops when the model cannot be improved without overfitting the model.

Internal validation and calibration were performed using resampling with replacement techniques (bootstrapping) that incorporated the variable selection process. The variable selection procedure was repeated for all 1000 re-samples and the resultant coefficient estimates

of each bootstrap sample were calculated on the original data, and a calibration slope (CS) was estimated [27]. CS=1 indicates a perfectly fitted model. CS<1 indicates over-fitting of the model reflecting the need for shrinkage to be applied to the coefficients by multiplying the estimates to the CS [27]. The performance of the prediction model was assessed using the area under the receiver operating characteristic curve (AUC). The AUCs were corrected for optimism by an internal validation procedure [28].

To address the multiple comparisons problem, adjustment for false discovery rate (FDR) was performed using the Benjamini–Hochberg procedure [29]. The FDR-adjusted two-sided *p*-value of <0.05 was considered significant. Statistical analysis was performed using ‘R’ (R Development Core Team), mainly, the *rms* package [28].

RESULTS

Data and Symptom Description

Distributions of clinical variables including the medication intake status are shown in Table 1. Table 2 shows the distribution of patients’ symptom grades at the end of treatment, 18-month, 36-month and 54-month follow-up and the distribution of peak incidence. The rate of Grade ≥ 2 symptoms for RADAR participants trial is low as discussed in previous publications [15, 16]. The evolution of urinary symptoms for each patient is presented in Appendix-B.

Principal components

About 89% of the variability of DSH is described by the first two principal components (PCs). Because the third PC explained less than 5% of variation, only the first two PCs (PC1 and PC2) were retained. The correlation of PC1 and PC2 to dose-surface indices are illustrated in Fig. 1. Briefly, PC1 is correlated with relative bladder surface receiving low and intermediate dose and has high correlation to the mean dose ($\rho=1$) while PC2 correlates mostly to the high doses.

Univariate outcome analysis

Odds ratios for factors studied to affect the symptom by univariate analysis are shown in Appendix-C. Baseline were found to be consistently predictive across most endpoints. Several clinical factors were found to have sustained impact (≥ 2 time points) on specific symptoms; BMI, non-insulin dependent diabetes mellitus (NIDDM) and smoking status for dysuria, hypoglaecemic agent intake for haematuria, cerebrovascular condition and alcohol intake for incontinence and hypertension and bladder volume for frequency. For dosimetric factors only PC1 was found to be important.

Variable selection and multivariate analysis

Hypertension, dyslipidaemia, NIDDM and bladder volume were correlated to the ACE intake (Spearman's rho, $\rho=0.57$), statin ($\rho=0.78$), hypoglycaemic agents ($\rho=0.69$) and PC1 ($\rho=-0.71$), respectively. Previous studies have suggested the association of hypertension to treatment-related symptoms may relate to the medication intake [7] while Wedlake et al. shown the reduction of treatment-related symptoms with the intake of statin and ACE [13] - therefore, the comorbidities were not included in the multivariate models. NIDDM, however, was included due to the impact previously shown [9, 10]. The negative correlation between the bladder volume and the dosimetric factor PC1 is expected due to the inclusion of larger relative bladder volume in the high dose region in patients with smaller/empty bladder [30]. As post-treatment symptomology is more logically explained by the bladder dosimetry rather than the

bladder size itself, only PC1 is included as a candidate. IDDM, collagen disorder, thyroid disorder and steroid intake were excluded not included due to the low prevalence (<5%).

In the prevalence multivariate analysis, the most predictive parameters were found to be the baseline symptoms (Table 3). Even so, the strength of baseline symptoms to predict dysuria diminishes for longer follow-up; Dys₅₄ and Incont₅₄. Also, the baseline symptoms do not significantly affect Haem_{acute}, Haem₃₆, Haem₅₄. NIDDM is the only factor consistently affecting dysuria across all time points. NIDDM significantly affects Dys₃₆ (odds ratio (OR)=3.30) and Dys₅₄ (OR=6.00), and included in the model for Dys_{acute} (OR=1.51, $p=0.107$), Dys₁₈ (OR=2.21, $p=0.079$). NIDDM is also selected for Haem₁₈. Increasing age significantly associated with decreasing Dys_{acute} (OR= 0.96/year) and Dys₅₄ (OR=0.91/year). Several factors were significantly associated with specific endpoints at specific time points; cerebrovascular condition increases the risk of Incont₁₈ (OR=4.88) and Freq₅₄ (OR=3.18), ECOG status of 1 is associated with a higher risk of Freq₃₆ (OR=2.17), NSAIDs intake increase the risk of Dys₅₄ (OR=4.25) and PC1 is associated with Freq_{acute} (OR=1.07/unit). PC1 shows a trend toward significance for Freq₅₄ (OR=1.08/unit, $p=0.053$). In the peak symptoms multivariate analysis (Table 4), similarly strong impacts of the baseline symptoms were found. In addition, smoking status (current vs never, OR=4.74) and bowel condition (OR=3.57) are significantly predictive of dysuria while cerebrovascular condition (OR=4.00) impacts the incontinence incidence.

Adjustments for optimism were made to not exaggerate the ability of the model to predict the outcome for new, independent observations. The internally validated discriminative ability yielded AUCs between 0.467 and 0.794, lower for endpoints without a significant predictor. Calibration slopes between 0.548 and 0.780 indicate that in case of replication of this analysis the resulting coefficients of the final model are on average smaller by that factor.

DISCUSSION

There is increasing evidence that urinary symptoms affect more patients than rectal symptoms in patients treated with radiotherapy for prostate carcinoma [1]. Understanding the impact of dosimetric and clinical factors on urinary symptoms after radiotherapy is crucial to help the decision making process for a more tailored treatment and patient care [2]. Data from RADAR, with a sufficiently large patient cohort and with long follow-up, is suitable for derivation of such evidence.

We have reported on the impact of dosimetric and clinical factors including medication intake on the prevalence and incidence of urinary symptoms following prostate radiotherapy. An analysis of symptoms by prevalence, including the effects of trial arm and radiotherapy dose prescription group for the RADAR trial, has recently been presented [16]. Combination of different symptoms into grades (e.g. RTOG scale as in [3, 9, 11, 12]) has the potential to obscure relevant associations if individual symptoms have different pathophysiological origins, thus, symptoms were atomised. We indeed found several factors which were influencing a specific urinary symptom and not others, facilitating a more symptom-specific pathophysiological understanding.

In assessing the effects following radiotherapy, there are some circumstances almost unique to urinary symptoms. The prevalence of lower urinary tract symptoms, sometimes indistinguishable from those related to treatment, is increasing with advancing age [2, 31].

Furthermore, the amelioration of the pre-treatment urinary symptoms after treatment is common and clinically relevant [32, 33]. The treatment-related urinary symptoms also show significant levels of reversibility [25, 26]. Given the circumstances surrounding the urinary symptoms, the use of cumulative or actuarial incidence alone may misrepresent and overestimate the actual burden [25, 26]. Thus, the current study used the prevalence at specific time points in addition to the peak incidence.

Baseline symptoms were found to offer the strongest predictive value for incontinence and frequency across all time points and peak incidence, consistent with previous reports [11, 12]. However, as seen via analysis of urinary symptoms in isolation, the effect of baseline is not uniformly strong across all symptom types. Dysuria and haematuria at baseline are less important factors to the respective long-term prevalence. The diminishing importance of baseline symptoms for certain endpoints is potentially related to the improvement of the symptoms after radiotherapy treatment shown here and similarly reported by others [26, 32-34]. Related to this, increasing age is associated with lower risk for dysuria which might be associated to the shrinkage of benign hypertrophic prostate after radiotherapy treatment which is more prevalent in older patients [35].

Probably the most important advantage of the current study was the availability of prospectively collected data on comorbidities, medication intake and lifestyle factors. Only diabetes is shown to have persistent effect on a specific symptom (i.e.; dysuria) across all time points. Diabetes has already been reported to increase the likelihood of delayed radiation-induced urinary morbidity [9, 10]. The impact, however, was not found by some others [7, 8]. The effect of diabetes to treatment-related urinary symptoms has been associated with the weakened ability to heal tissue damage because of microvascular changes related to the chronic pathological processes [9, 36]. This study adds two important points to the knowledge; first, with the analysis based on prevalence which reduces the accumulation of transient symptoms, we have established that the effect of NIDDM is in fact persistent; second, the effect is strong for dysuria and potentially haematuria but not incontinence and frequency suggesting different pathological pathways.

Significantly worse peak dysuria were found for current smokers compared to those who never smoked. Observations by Peeters et al. [11] of increasing late urinary symptoms in patients who smoke was dismissed as a random discovery, however, the current study made a similar finding suggesting that the relationship is potentially relevant. The impact of smoking has previously been found for rectal toxicity associated with amplified vascular damage, tissue hypoxia and fibrosis [37].

PC1, which was significantly associated with urinary frequency, is correlated to the mean dose suggesting the importance of global dose distribution for this endpoint as opposed to maximum dose frequently suggested to play a bigger role in causation of urinary symptoms [3, 4]. Radiotherapy has been associated with reduction in bladder capacity and decrease in bladder volume at first sensation [38]. This study has put forward the potential of the physiological changes to be related to the bladder dose-surface information requiring a more detailed urodynamic study. Despite that, the relationships between PCs and other urinary symptoms were poor. There are several potential explanations; first, the PCs which summarise most of the DSH variances into two variables do limit the search space for potential correlations. Limiting the search space has the benefit of generating a general understanding of the overall impact of DSH features whilst preventing random discovery associated with searching for

optimal cutpoints in the high dimensional space of the original DSHs. However, correlating symptoms to specific dose-surface cutpoints may provide specific and stronger dosimetry-symptom relationships. Second, due to generally open bladder filling protocol in the trial where centres may decide to use empty or full bladder, there were large variations of bladder volume. The relative surface of bladder receiving a particular dose threshold may be impacted by the bladder filling due to the expansion of the bladder, known to be anisotropic, and this may influence the resultant dosimetric impact [39].

We identified cerebrovascular condition, worse ECOG status and NSAIDs intake as factors increasing the risk of specific urinary symptoms by multivariate analysis at a specific time. These factors, however, do not show associations in other time points studied and only cerebrovascular condition shows association in the incidence analysis. There are several ways to view these observations;

1. The impacts of these clinical factors may be temporally specific. Treatment-related radiotherapy injury is complex where the process of healing undergoes a series of events that are yet to be fully comprehended [36]. Conventionally, toxicity studies separate the events into two phases, acute and late, of which acute symptoms are defined as symptoms happening in the first 3 months after the end of treatment while late symptoms are defined as all symptoms occurring after that [11, 34]. It has been shown that the two phases do not share a similar set of predictors suggesting potentially different pathophysiological processes [11, 34]. However, in such analyses the late effects definition spans many years until the last follow-up which makes the understanding of the symptoms' evolution challenging. Distinct predictors between late symptoms occurring in the first 3 years and those occurring later has been illustrated by Fellin et. al. [40] on rectal incontinence and bleeding. Few, if any, have attempted to study the important predictors of urinary symptoms across more refined phases.
2. The reversibility of treatment-related urinary symptoms plays an important role [25, 26]. The improvements due to the natural healing process or successful management may introduce fluctuation of association at different time points. The increased risk of dysuria for younger patients, for example, was strong at the end of radiotherapy treatment but not repeated until at 54-month follow-up suggesting the fluctuation across follow-up time.
3. The observations may also be fortuitous. As some of the observations are counterintuitive (e.g. higher risk for younger patients) or involving clinical factors rarely studied (e.g. cerebrovascular condition), there are needs for validation from other datasets.

The impact of other comorbidities and medication intake, found to be significant in other studies, was not identified in this cohort. Examples include the protective effect of hypertension which was suggested to be associated to antihypertensive medication intake [7], and exacerbation of haematuria with anticoagulant intake [2, 10].

Despite several strengths, this study has several limitations. The clinical factors and medication intake were only acquired at randomization. It is likely that patients were diagnosed with other comorbidities and prescribed with different types of medication at any time after that. It is also acknowledged that a DSH derived from a single treatment plan is only a surrogate parameter for the actual dose distribution received by the patient [41].

CONCLUSION

Several parameters impacting specific urinary symptoms after prostate cancer radiotherapy were identified. Baseline symptoms and NIDDM were found to have sustained impacts across all time points while age and PC1 were repeated in more than one time point. Other associations found to be significant are not repeated at different time points suggesting poorer or transient impacts. Different impacts of clinical factors from prevalence and incidence analysis providing a complementary view for urinary symptoms prediction.

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- [1] Zelefsky MJ, Levin EJ, Hunt M, Yamada Y, Shippy AM, Jackson A, et al. Incidence of late rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2008;70:1124-9.
- [2] Viswanathan AN, Yorke ED, Marks LB, Eifel PJ, Shipley WU. Radiation dose-volume effects of the urinary bladder. *Int J Radiat Oncol Biol Phys.* 2010;76:S116-22.
- [3] Cheung MR, Tucker SL, Dong L, de Crevoisier R, Lee AK, Frank S, et al. Investigation of bladder dose and volume factors influencing late urinary toxicity after external beam radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2007;67:1059-65.
- [4] Harsolia A, Vargas C, Yan D, Brabbins D, Lockman D, Liang J, et al. Predictors for chronic urinary toxicity after the treatment of prostate cancer with adaptive three-dimensional conformal radiotherapy: dose-volume analysis of a phase II dose-escalation study. *Int J Radiat Oncol Biol Phys.* 2007;69:1100-9.
- [5] Carillo V, Cozzarini C, Rancati T, Avuzzi B, Botti A, Borca VC, et al. Relationships between bladder dose-volume/surface histograms and acute urinary toxicity after radiotherapy for prostate cancer. *Radiother Oncol.* 2014;111:100-5.
- [6] Heemsbergen WD, Al-Mamgani A, Witte MG, van Herk M, Pos FJ, Lebesque JV. Urinary obstruction in prostate cancer patients from the Dutch trial (68 Gy vs. 78 Gy): relationships with local dose, acute effects, and baseline characteristics. *Int J Radiat Oncol Biol Phys.* 2010;78:19-25.
- [7] Barnett GC, De Meerleer G, Gulliford SL, Sydes MR, Elliott RM, Dearnaley DP. The Impact of Clinical Factors on the Development of Late Radiation Toxicity: Results from the Medical Research Council RT01 Trial (ISRCTN47772397). *Clin Oncol.* 2011;23:613-24.
- [8] Cozzarini C, Fiorino C, Da Pozzo LF, Alongi F, Berardi G, Bolognesi A, et al. Clinical factors predicting late severe urinary toxicity after postoperative radiotherapy for prostate carcinoma: a single-institute analysis of 742 patients. *Int J Radiat Oncol Biol Phys.* 2012;82:191-9.

- [9] Herold DM, Hanlon AL, Hanks GE. Diabetes mellitus: a predictor for late radiation morbidity. *Int J Radiat Oncol Biol Phys.* 1999;43:475-9.
- [10] Mathieu R, Arango JD, Beckendorf V, Delobel JB, Messai T, Chira C, et al. Nomograms to predict late urinary toxicity after prostate cancer radiotherapy. *World J Urol.* 2013.
- [11] Peeters ST, Heemsbergen WD, van Putten WL, Slot A, Tabak H, Mens JW, et al. Acute and late complications after radiotherapy for prostate cancer: results of a multicenter randomized trial comparing 68 Gy to 78 Gy. *Int J Radiat Oncol Biol Phys.* 2005;61:1019-34.
- [12] Karlsdottir A, Muren LP, Wentzel-Larsen T, Dahl O. Late gastrointestinal morbidity after three-dimensional conformal radiation therapy for prostate cancer fades with time in contrast to genitourinary morbidity. *Int J Radiat Oncol Biol Phys.* 2008;70:1478-86.
- [13] Wedlake LJ, Silia F, Benton B, Lalji A, Thomas K, Dearnaley DP, et al. Evaluating the efficacy of statins and ACE-inhibitors in reducing gastrointestinal toxicity in patients receiving radiotherapy for pelvic malignancies. *Eur J Cancer.* 2012;48:2117-24.
- [14] <http://clinicaltrials.gov/show/NCT00193856>.
- [15] Denham JW, Wilcox C, Joseph D, Spry NA, Lamb DS, Tai K-H, et al. Quality of life in men with locally advanced prostate cancer treated with leuprorelin and radiotherapy with or without zoledronic acid (TROG 03.04 RADAR): secondary endpoints from a randomised phase 3 factorial trial. *Lancet Oncol.* 2012;13:1260-70.
- [16] Denham JW, Wilcox C, Lamb DS, Spry NA, Duchesne G, Atkinson C, et al. Rectal and urinary dysfunction in the TROG 03.04 RADAR trial for locally advanced prostate cancer. *Radiother Oncol.* 2012;105:184-92.
- [17] Haworth A, Kearvell R, Greer PB, Hooton B, Denham JW, Lamb D, et al. Assuring high quality treatment delivery in clinical trials - Results from the Trans-Tasman Radiation Oncology Group (TROG) study 03.04 "RADAR" set-up accuracy study. *Radiother Oncol.* 2009;90:299-306.
- [18] Kearvell R, Haworth A, Ebert MA, Murray J, Hooton B, Richardson S, et al. Quality improvements in prostate radiotherapy: Outcomes and impact of comprehensive quality assurance during the TROG 03.04 'RADAR' trial. *J Med Imaging Radiat Oncol.* 2013;57:247-57.
- [19] Ebert MA, Haworth A, Kearvell R, Hooton B, Coleman R, Spry N, et al. Detailed review and analysis of complex radiotherapy clinical trial planning data: evaluation and initial experience with the SWAN software system. *Radiother Oncol.* 2008;86:200-10.
- [20] Ebert MA, Haworth A, Kearvell R, Hooton B, Hug B, Spry NA, et al. Comparison of DVH data from multiple radiotherapy treatment planning systems. *Phys Med Biol.* 2010;55:N337-46.
- [21] Bentzen SM, Dorr W, Gahbauer R, Howell RW, Joiner MC, Jones B, et al. Bioeffect modeling and equieffective dose concepts in radiation oncology--terminology, quantities and units. *Radiother Oncol.* 2012;105:266-8.
- [22] Skala M, Rosewall T, Dawson L, Divanbeigi L, Lockwood G, Thomas C, et al. Patient-assessed late toxicity rates and principal component analysis after image-guided radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2007;68:690-8.
- [23] Dawson LA, Biersack M, Lockwood G, Eisbruch A, Lawrence TS, Ten Haken RK. Use of principal component analysis to evaluate the partial organ tolerance of normal tissues to radiation. *Int J Radiat Oncol Biol Phys.* 2005;62:829-37.
- [24] Lent soma scales for all anatomic sites. *Int J Radiat Oncol Biol Phys.* 1995;31:1049-91.
- [25] Schmid MP, Potter R, Bombosch V, Sljivic S, Kirisits C, Dorr W, et al. Late gastrointestinal and urogenital side-effects after radiotherapy--incidence and prevalence. Subgroup-analysis within the prospective Austrian-German phase II multicenter trial for localized prostate cancer. *Radiother Oncol.* 2012;104:114-8.

- [26] Christie D, Denham J, Steigler A, Lamb D, Turner S, Mameghan H, et al. Delayed rectal and urinary symptomatology in patients treated for prostate cancer by radiotherapy with or without short term neo-adjuvant androgen deprivation. *Radiother Oncol.* 2005;77:117-25.
- [27] Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology.* 2010;21:128-38.
- [28] Harrell FE. rms: Regression Modeling Strategies. R package version 4.2-0. . 2014.
- [29] Benjamini Y, Hochberg Y. Controlling the False Discovery Rate - a Practical and Powerful Approach to Multiple Testing. *J Roy Stat Soc B Met.* 1995;57:289-300.
- [30] Pinkawa M, Asadpour B, Gagel B, Piroth MD, Holy R, Eble MJ. Prostate position variability and dose-volume histograms in radiotherapy for prostate cancer with full and empty bladder. *Int J Radiat Oncol Biol Phys.* 2006;64:856-61.
- [31] Malmsten UG, Molander U, Pecker R, Irwin DE, Milsom I. Urinary incontinence, overactive bladder, and other lower urinary tract symptoms: a longitudinal population-based survey in men aged 45-103 years. *Eur Urol.* 2010;58:149-56.
- [32] Malik R, Jani AB, Liauw SL. External beam radiotherapy for prostate cancer: urinary outcomes for men with high International Prostate Symptom Scores (IPSS). *Int J Radiat Oncol Biol Phys.* 2011;80:1080-6.
- [33] Ghadjar P, Jackson A, Spratt DE, Oh JH, Munck af Rosenschold P, Kollmeier M, et al. Patterns and predictors of amelioration of genitourinary toxicity after high-dose intensity-modulated radiation therapy for localized prostate cancer: implications for defining postradiotherapy urinary toxicity. *Eur Urol.* 2013;64:931-8.
- [34] Fonteyne V, Villeirs G, Lumen N, De Meerleer G. Urinary toxicity after high dose intensity modulated radiotherapy as primary therapy for prostate cancer. *Radiother Oncol.* 2009;92:42-7.
- [35] Garraway WM, Collins GN, Lee RJ. High prevalence of benign prostatic hypertrophy in the community. *Lancet.* 1991;338:469-71.
- [36] Denham JW, Hauer-Jensen M. The radiotherapeutic injury--a complex 'wound'. *Radiother Oncol.* 2002;63:129-45.
- [37] Alsadius D, Hedelin M, Johansson KA, Pettersson N, Wilderang U, Lundstedt D, et al. Tobacco smoking and long-lasting symptoms from the bowel and the anal-sphincter region after radiotherapy for prostate cancer. *Radiother Oncol.* 2011;101:495-501.
- [38] Choo R, Do V, Herschorn S, DeBoer G, Danjoux C, Morton G, et al. Urodynamic changes at 18 months post-therapy in patients treated with external beam radiotherapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys.* 2002;53:290-6.
- [39] Pinkawa M, Asadpour B, Siluschek J, Gagel B, Piroth MD, Demirel C, et al. Bladder extension variability during pelvic external beam radiotherapy with a full or empty bladder. *Radiother Oncol.* 2007;83:163-7.
- [40] Fellin G, Rancati T, Fiorino C, Vavassori V, Antognoni P, Baccolini M, et al. Long term rectal function after high-dose prostatecancer radiotherapy: results from a prospective cohort study. *Radiother Oncol.* 2014;110:272-7.
- [41] Hatton JA, Greer PB, Tang C, Wright P, Capp A, Gupta S, et al. Does the planning dose-volume histogram represent treatment doses in image-guided prostate radiation therapy? Assessment with cone-beam computerised tomography scans. *Radiother Oncol.* 2011;98:162-8.

Table 1: Distributions of investigated variables. Continuous distributions are specified as mean $\pm$ standard deviation (range), categorical variables are specified as number of patients (%). Not all patients available for all assessments due to missing data, exclusions etc.

Factors		Missing
Physical & Trial factors		
Age	69 $\pm$ 7(49-85) years	3
BMI	27.98 $\pm$ 4.12 (17.17-45.77) kg/m ²	22
ECOG Performance Status (=1)	123 (16%)	1
Arm	A (191), B (187), C (192), D (184) (refer to [15, 16])	0
Bladder volume	219.4 $\pm$ 89.9 (61.0-561.7) cm ³	13
Comorbidities		
Cardiovascular condition	217 (29)	0
Peripheral vascular condition	44 (6)	0
Cerebrovascular condition	37 (5)	0
Hypertension	353 (49)	1
Dyslipidaemia	248 (33)	2
NIDDM	92 (12)	2
IDDM	14 (2)	0
Respiratory disorder	99 (13)	0
Bowel disorder	91 (12)	1
Dermatological disorder	52 (7)	1
Collagen disorder	15 (2)	1
Bone or calcium metabolism disorder	66 (9)	1
Haematological disorder	11 (1)	1
Thyroid disorder	24 (3)	1
Medication intake		
Insulin	14 (2)	6
Hypoglycaemic agents	55 (7)	7
ACE Inhibitor	240 (32.1)	8
Statin	221 (29.6)	8
Steroids	24 (3)	8
NSAID	136 (18.2)	6
Anti-coagulant	120 (16.0)	6
Antioxidants, flavonoids, phyto-oestrogens or selenium	25 (3)	17
Lifestyle factors		

Smoking status	Never 274 (36) ; Previous 380 (50) ; Current 99 (13)	1
Alcohol intake	None 100 (13) ; Occasional 279 (37) ; Regular 370 (49)	5
No. of patients with no missing information: 711		

Abbreviations; OR- Odds ratio; BMI - body mass index; ECOG - ECOG Performance Status; NIDDM – non-insulin dependent diabetes mellitus; IDDM – insulin dependent diabetes mellitus; ACE - angiotensin-converting-enzyme; NSAID – non-steroidal anti-inflammatory drugs; PC- principal component.

Table 2: Number of patients in each grade of symptoms at the end of treatment and at 18-, 36- and 54-month follow-ups and the peak late symptom.

Symptom	Grade	End of RT	Month 18	Month 36	Month 54	Peak late (Grade≥2, dichotomised)
Dysuria	0	361	655	599	459	693
	1	252	45	31	20	53
	2	106	12	5	7	
	3	32	4	0	1	
Haematuria	0	734	702	620	469	729
	1	15	13	15	11	17
	2	3	1	2	4	
	3	0	0	0	1	
Incontinence	0	648	665	582	444	657
	1	59	37	41	29	89
	2	42	14	15	12	
	3	3	0	1	1	
Frequency	0	128	477	458	349	530
	1	316	186	154	110	216
	2	249	51	21	27	
	3	59	2	3	0	

Table 3: Multivariate analysis examining relationship between the dosimetry, clinical factors and medication intake to the prevalence of urinary symptoms (Grade ≥ 1) at the end of treatment, 18-, 36- and 54-month follow-up post randomisation. Discriminative values measured by the optimism-corrected area under the receiver operating characteristic curve. The calibration slopes quantify the optimism of coefficients.

Note: Significant factors are bold, *the respective odds ratio can be calculated with the normal convention, $e^{\text{coefficient}}$ and the 95% confidence interval= $e^{(\text{coefficient} \pm 1.96 \cdot \text{SE})}$, †calibration slope describes the optimism of the coefficients, calibration slope<1 suggest overoptimism, to calculate for optimism-adjusted coefficients = coefficient $\times$ calibration slope; estimate is based on 1 grade increase (Baseline), 1 vs 0 (ECOG), per unit (PC1, PC2), per kgm^{-2} (BMI), year (age), yes vs no (all others); abbreviations - S.E – standard error; P – false-discovery-rate-controlled p -value; ACE - angiotensin-converting-enzyme; BMI - body mass index; ECOG - ECOG Performance Status; NSAID – non-steroidal anti-inflammatory drugs; PC- principal component; prev. – previous; cond. – condition; AUCa- Apparent area under the receiver operating characteristic curve (AUC); AUCo- Optimism-adjusted AUC.

End of treatment					18 months				36 months				54 months			
Endpoint	Variable	Coef.*	S.E	P	Variable	Coef.	S.E	P	Variable	Coef.	S.E	P	Variable	Coef.	S.E	P
Dysuria	Baseline	0.999	0.179	0.002	Baseline	0.739	0.244	0.014	NIDDM			0.034	NSAIDs	1.447	0.465	0.014
	Age	-0.042	0.011	0.002	BMI	0.069	0.031	0.073	Baseline			0.042	NIDDM	1.791	0.592	0.015
	Bowel cond.	0.425	0.219	0.104	NIDDM	0.793	0.354	0.079	Smoking status				Age	-0.097	0.037	0.042
	NIDDM	0.413	0.222	0.107	Cerebrovascular	0.924	0.485	0.104	prev. vs never	0.400	0.439	0.382	Cerebrovascular	1.533	0.664	0.073
	PC2	0.115	0.062	0.108					current vs never	1.171	0.555	0.084	Baseline	0.796	0.365	0.081
	ECOG	0.289	0.194	0.167					Cerebrovascular	1.064	0.694	0.159	ACE inhibitor	0.939	0.468	0.104
	BMI	-0.025	0.018	0.171					Arm				Statin	-1.109	0.556	0.104
									B vs A	-0.083	0.519	0.873	Respiratory cond.	0.964	0.540	0.142
									C vs A	0.369	0.462	0.430	Anticoagulant	0.898	0.591	0.167
									D vs A	-1.688	0.807	0.086				
		AUCa=0.631	†Calibration slope=0.747		AUCa=0.643	Calibration slope=0.625		AUCa= 0.767	Calibration slope = 0.567		AUCa=0.822	Calibration slope=0.599				
		AUCo=0.594			AUCo=0.556			AUCo= 0.663			AUCo=0.727					
Haematuria	Age (/year)	-0.053	0.035	0.176	NIDDM	1.630	0.648	0.073	PC2	-0.638	0.419	0.161	Bowel cond.	1.129	0.624	0.150
					Baseline	2.487	0.964	0.104	PC1	-0.134	0.091	0.165				
					PC1	0.192	0.090	0.114								
		AUCa=0.608	Calibration slope=0.427		AUCa=0.873	Calibration slope=0.677		AUCa=0.669	Calibration slope =0.458		AUCa=0.576	Calibration slope=0.488				
		AUCo=0.467			AUCo=0.794			AUCo=0.532			AUCo=0.471					
Incontinence	Baseline	1.267	0.329	0.002	Baseline	1.069	0.390	0.010	Baseline	1.203	0.336	0.003	Baseline	1.075	0.430	0.050
	Age (/year)	0.043	0.018	0.053	Cerebrovascular	1.586	0.493	0.036					ACE inhibitor	0.690	0.359	0.104
	BMI (/kgm ⁻²)	0.041	0.026	0.148	BMI	0.079	0.035	0.061					Cardiovascular	-0.910	0.484	0.104
	Arm				ECOG	0.716	0.371	0.104					Respiratory cond.	0.630	0.420	0.165
	B vs A	-0.278	0.319	0.400	PC2	-0.334	0.183	0.129								
	C vs A	-0.527	0.329	0.148	Cardiovascular	-0.684	0.393	0.148								
	D vs A	0.240	0.288	0.418												
		AUCa= 0.665	Calibration slope = 0.636		AUCa=0.697	Calibration slope=0.640		AUCa=0.568	Calibration slope=0.596		AUCa=0.651	Calibration slope=0.548				
		AUCo= 0.591			AUCo=0.609			AUCo=0.475			AUCo=0.555					
Frequency	Baseline	0.645	0.114	<0.001	Baseline	0.815	0.130	<0.001	Baseline	0.773	0.145	<0.001	Baseline	0.893	0.163	<0.001
	PC1	0.068	0.021	0.008	Arm				ECOG	0.731	0.238	0.012	Cerebrovascular	1.158	0.444	0.040
	NSAIDs	0.376	0.184	0.094	B vs A	-0.242	0.258	0.370	Smoking status				PC1	0.075	0.032	0.064
	ACE inhibitor	-0.247	0.151	0.148	C vs A	0.522	0.238	0.075	current vs never	0.416	0.316	0.208	Anticoagulant	-0.694	0.343	0.098
	PC2	0.093	0.058	0.148	D vs A	0.670	0.235	0.020	prev. vs never	0.426	0.210	0.095	Bone/calcium metabolism disorder	0.624	0.355	0.129
	ECOG	0.289	0.191	0.161	BMI	0.035	0.020	0.129	NSAIDs	0.376	0.238	0.137				
		AUCa=0.633	Calibration slope =0.780		AUCa= 0.663	Calibration slope = 0.755		AUCa=0.678	Calibration slope=0.765		AUCa=0.682	Calibration slope=0.743				
		AUCo=0.602			AUCo= 0.620			AUCo=0.633			AUCo=0.630					

Table 4: Multivariate analysis examining relationship between the dosimetry, clinical factors and medication intake to the incidence of late urinary symptoms (Grade ≥ 2).

Endpoint	Variable	Peak incidence Grade >1		
		Coef.	S.E	P
Dysuria	Smoking status			
	<i>prev. vs never</i>	0.330	0.384	0.430
	<i>current vs never</i>	1.562	0.456	0.008
	Bowel cond.	1.272	0.374	0.011
	Baseline	0.841	0.285	0.048
	BMI	0.069	0.036	0.104
	Statin	0.504	0.327	0.164
	Peripheral vascular condition	-1.578	1.068	0.167
	<hr/>			
	<i>AUCa=0.738</i>	<i>Calibration slope= 0.662</i>		
Haematuria	Bowel cond.	1.122	0.577	0.104
	Statin	0.886	0.525	0.129
	BMI	0.088	0.056	0.148
	<hr/>			
	<i>AUCa=0.718</i>	<i>Calibration slope= 0.537</i>		
	<i>AUCo=0.592</i>			
Incontinence	Baseline	1.341	0.367	0.003
	Cerebrovascular	1.385	0.434	0.010
	Anticoagulant	-0.611	0.381	0.148
	<hr/>			
	<i>AUCa=0.608</i>	<i>Calibration slope = 0.651</i>		
Frequency	<i>AUCo=0.532</i>			
	Baseline	0.835	0.136	<0.001
	Age	0.033	0.014	0.053
	ECOG	0.491	0.229	0.081
	PC1	0.049	0.026	0.104
	Arm			
	B vs A	-0.317	0.267	0.254
	C vs A	0.442	0.245	0.116
	D vs A	0.314	0.251	0.230
	<hr/>			
	<i>AUCa= 0.693</i>	<i>Calibration slope = 0.760</i>		
	<i>AUCo= 0.647</i>			

Note: Refer Table 3 for abbreviations and notes.

Fig. 1: Correlation, ρ of the first and second principal components (PC1 and PC2) to EQD2. Percent variance described by eigenvector is shown in parentheses.

Appendix-A: Correlation of dose-surface indices

Appendix-B: Profile of patient-wise i) dysuria (ii) haematuria, (iii) incontinence and (iv) frequency after prostate cancer radiotherapy for 754 patients (distributed vertically) ordered by baseline symptoms at the end of radiotherapy (End), each follow-up visit (9-84-month follow-up) and the peak late grade (dys.max, haem.max, incont.max, freq.max). The colours indicate the grade. The colours indicate the grade of symptoms, white: no data.

i)

ii)

iii)

Appendix-C: Univariate analysis of all clinical factors studied.

Factor	DyS _{acute}	DyS ₁₈	DyS ₃₆	DyS ₅₄	Haem _{acute}	Haem ₁₈	Haem ₃₆	Haem ₅₄	Incont _{acute}	Incont ₁₈	Incont ₃₆	Incont ₅₄	Freq _{acute}	Freq ₁₈	Freq ₃₆	Freq ₅₄
Physical factors	Odds ratio															
Age (per year)	0.97	0.99	0.98	0.96	0.95	0.95	0.97	0.99	1.04	1.01	1.02	1.01	1.00	1.01	1.01	1.02
BMI (per 1kgm ⁻²)	0.99	1.09	1.03	1.11	1.04	1.08	1.06	1.07	1.04	1.08	1.05	1.06	0.98	1.02	1.00	1.01
ECOG (1 vs 0)	1.22	1.72	1.76	0.86	1.02	0.38	1.57	0.34	1.34	1.60	1.06	0.85	1.39	1.40	2.42	1.30
Bladder volume (per 10 cm ³)	1.00	0.99	1.01	1.00	1.02	0.95	1.02	1.03	0.99	0.98	0.99	0.99	0.98	0.98	0.97	0.97
Comorbidities																
Baseline	2.68	2.09	2.09	1.93	-	11.43	-	-	3.45	3.19	3.76	3.03	1.93	2.12	2.27	2.42
Cardiovascular condition	1.04	1.16	0.96	1.34	1.23	0.41	1.37	0.94	0.99	0.76	0.78	0.53	0.89	0.85	0.96	0.97
Peripheral vascular condition	0.74	0.82	0.46	1.30	2.10		1.04	1.17	1.35	0.66	0.58	0.82	0.77	0.77	1.37	0.99
Cerebrovascular condition	0.87	2.39	2.23	4.41	1.13	1.46	1.37	1.27	2.23	3.74	1.69	2.30	1.42	1.80	1.88	3.08
Hypertension	0.93	1.31	1.06	2.33	0.72	1.10	2.22	0.56	1.09	1.39	0.99	1.15	1.00	1.38	1.28	1.53
Dyslipidaemia	1.06	1.24	1.35	1.14	1.64	2.01	1.33	0.94	1.53	1.26	1.60	1.42	1.23	1.24	1.21	1.27
Diabetes - IDDM	0.28	0.97	1.66	-	-	-	-	-	1.16	-	1.01	-	0.72	0.18	0.25	3.04
Diabetes - NIDDM	1.37	2.20	2.68	2.65	1.46	4.30	1.62	0.58	1.36	1.62	1.21	1.48	0.81	1.19	1.18	0.97
Respiratory disorder	0.83	1.42	0.55	1.66	0.83	0.49	0.84	1.36	1.46	1.22	0.87	2.07	0.98	0.78	0.63	1.30
Bowel disorder	1.36	1.39	1.85	0.87	0.90	1.24	0.98	2.59	1.28	1.21	1.63	1.00	1.29	0.92	1.20	1.14
Dermatological disorder	0.93	1.17	0.74	0.98	-	-	-	0.84	0.66	0.81	0.44	1.82	1.34	1.18	0.99	1.12
Collagen disorder	1.04	2.80	3.35	5.22	-	-	-	4.19	1.65	-	-	1.68	1.20	1.09	0.82	0.94
Bone or calcium metabolism disorder	1.29	0.92	1.08	1.33	0.60	1.71	-	-	0.59	1.13	1.41	1.89	1.43	1.15	1.34	1.84
Haematological disorder	0.69	-	-	-	-	-	-	-	1.26	1.41	-	2.36	1.16	0.53	1.20	1.74
Thyroid disorder	0.95	2.66	1.86	2.70	1.80	-	1.86	4.42	0.56	1.28	-	-	1.21	1.12	0.58	1.37
Medication intake																
Insulin	0.26	0.87	1.50	-	-	-	-	-	1.64	-	0.90	-	0.71	0.34	0.49	2.06
Hypoglycaemic agents	1.47	2.16	2.25	0.58	2.62	3.74	2.90	1.03	1.87	1.10	2.25	1.65	0.92	1.10	1.43	1.10
ACE Inhibitor	0.98	1.59	2.05	1.99	0.60	0.85	1.99	0.76	1.10	1.87	1.31	1.61	0.77	1.09	0.80	1.40
Statin	1.12	1.01	0.97	0.90	0.91	1.77	2.02	1.04	1.36	1.20	1.30	1.42	1.00	1.15	1.08	1.06
Steroids	0.70	0.49	1.66	3.29	1.78	-	0.78	1.62	1.81	1.40	1.73	2.17	1.25	0.58	0.76	1.44
NSAID	1.17	1.06	1.33	2.97	0.89	0.33	1.42	1.42	0.97	1.20	1.07	1.00	1.23	1.22	1.26	1.32
Anti-coagulant	1.13	1.44	1.29	1.61	0.65	0.84	1.60	1.35	1.15	1.09	0.82	0.77	1.16	1.14	0.86	0.69
Antioxidants, flavanoids, phyto-oestrogens or selenium	1.13	-	0.73	5.05	1.69	-	1.66	1.70	0.53	-	1.02	-	0.98	1.04	1.18	2.08
Lifestyle factors																
Smoking status, (previous vs never)	1.11	1.97	1.73	0.82	0.89	2.34	0.77	-	1.08	1.49	1.36	0.98	1.13	1.15	1.49	0.93
(current vs never)	1.61	1.95	2.79	0.52	2.65	2.14	1.45	-	1.36	1.72	1.55	0.99	1.13	1.25	1.75	0.98
Alcohol intake (occasional vs no)	0.98	1.03	1.38	0.95	0.43	2.11	0.42	2.95	0.49	0.39	0.71	0.60	1.17	1.26	1.03	0.70
(regular vs no)	1.07	1.63	1.86	1.49	0.59	1.80	0.51	1.81	0.60	0.70	0.81	0.60	1.02	1.05	1.15	0.82
Dosimetric factors																
PC1 (per unit)	1.01	1.02	1.07	1.02	0.99	1.26	0.92	0.92	1.02	1.05	1.04	1.01	1.07	1.03	1.03	1.05

PC2 (per unit)	1.10	1.05	1.06	1.04	0.85	1.21	0.65	1.00	1.00	0.78	0.84	0.98	1.10	0.97	0.96	0.90
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	Dys _{peak}	Haem _{peak}	Incont _{peak}	Freq _{peak}
Physical factors				
Age (per year)	0.98	0.99	1.03	1.03
BMI (per 1kgm ⁻²)	1.06	1.11	1.02	1.01
ECOG (1 vs 0)	1.55	2.34	1.16	1.91
Bladder volume (per 10 cm ³)	0.99	1.03	1.01	0.97
Comorbidities				
Baseline	1.86	-	4.11	2.28
Cardiovascular condition	1.08	0.86	0.90	0.85
Peripheral vascular condition	0.30	2.17	0.75	0.96
Cerebrovascular condition	1.77	2.74	3.77	1.49
Hypertension	1.25	1.92	1.26	0.95
Dyslipidaemia	1.86	2.14	0.87	1.13
Diabetes - IDDM	-	-	0.67	0.22
Diabetes - NIDDM	1.31	0.49	1.07	0.80
Respiratory disorder	1.18	0.45	1.36	1.06
Bowel disorder	3.14	3.58	1.36	1.07
Dermatological disorder	0.60	2.07	1.40	1.13
Collagen disorder	1.01	3.34	0.56	1.38
Bone or calcium metabolism disorder	1.30	1.58	1.23	1.16
Haematological disorder	-	4.37	0.74	0.55
Thyroid disorder	3.97	4.38	-	0.51
Medication intake				
Insulin	-	-	1.49	0.22
Hypoglycaemic agents	1.68	0.92	1.12	0.58
ACE Inhibitor	1.44	1.69	1.38	0.83
Statin	1.51	2.50	1.10	0.97
Steroids	0.65	-	2.40	0.77
NSAID	1.34	1.02	1.20	1.36
Anti-coagulant	1.04	1.20	0.80	0.97
Antioxidants, flavanoids, phyto-oestrogens or selenium	1.27	-	0.70	0.68
Lifestyle factors				
Smoking status, (previous vs never)	1.61	0.91	1.06	1.12
(current vs never)	3.36	1.54	1.42	1.02
Alcohol intake (occasional vs no)	2.46	2.64	0.52	0.60
(regular vs no)	2.45	2.19	0.55	0.75
B vs A	2.19	1.38	0.88	0.84
C vs A	1.35	0.74	0.79	1.46
D vs A	1.18	1.06	1.12	1.47
Dosimetric factors				
PC1 (per unit)	1.02	1.01	0.96	1.06

PC2 (per unit)	0.94	0.72	1.05	1.07
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† Unless stated in parentheses, the odds ratios are the odds for patients with comorbidities/taking medication to patients who did not; - analysis did not reach convergence; the *p*-values were not adjusted for multiple comparisons as this analysis attempted to give an overview of the effect of the potential predictors; *p*<0.05 are bold. Abbreviations; BMI - body mass index; ECOG - ECOG Performance Status; NIDDM – non-insulin dependent diabetes mellitus; IDDM – insulin dependent diabetes mellitus; ACE - angiotensin-converting-enzyme; NSAID – non-steroidal anti-inflammatory drugs; PC- principal component