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Prostate cancer radiotherapy

Urinary symptoms following external beam radiotherapy of the prostate: Dose–symptom correlates with multiple-event and event-count models

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ABSTRACT

Background and purpose: This study aimed to compare urinary dose–symptom correlates after external beam radiotherapy of the prostate using commonly utilised peak-symptom models to multiple-event and event-count models which account for repeated events.

Materials and methods: Urinary symptoms (dysuria, haematuria, incontinence and frequency) from 754 participants from TROG 03.04-RADAR trial were analysed. Relative (R1–R75 Gy) and absolute (A60–A75 Gy) bladder dose-surface area receiving more than a threshold dose and equivalent uniform dose using exponent a (range: $a \in [1 \ldots 100]$) were derived. The dose–symptom correlates were analysed using; peak-symptom (logistic), multiple-event (generalised estimating equation) and event-count (negative binomial regression) models.

Results: Stronger dose–symptom correlates were found for incontinence and frequency using multiple-event and/or event-count models. For dysuria and haematuria, similar or better relationships were found using peak-symptom models. Dysuria, haematuria and high grade ($\geqslant 2$) incontinence were associated to high dose (R61–R71 Gy). Frequency and low grade ($\geqslant 1$) incontinence were associated to low and intermediate dose-surface parameters (R13–R41 Gy). Frequency showed a parallel behaviour ($a = 1$) while dysuria, haematuria and incontinence showed a more serial behaviour ($a = 4$ to $a \geqslant 100$). Relative dose-surface showed stronger dose–symptom associations.

Conclusions: For certain endpoints, the multiple-event and event-count models provide stronger correlates over peak-symptom models. Accounting for multiple events may be advantageous for a more complete understanding of urinary dose–symptom relationships.

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The seminal article by Viswanathan et al. in the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) report noted that the question of dose–response for urinary symptoms in prostate-cancer treatment has not been resolved [1]. Few studies assessing relevant dose–symptom correlates are available [2–8].

Commonly, cumulative incidence has been utilised in dose–symptom studies where an event comprises any symptoms above a predetermined level. This might not be optimal given the natural propensity of urinary symptoms, sometimes similar to treatment-related symptoms, to occur in an aged population [1,9] and significant reversibility either as the result of successful management or naturally [10,11]. Improvement from baseline symptoms, linked with contraction of both benign hypertrophic and malignant tissues, is common and clinically relevant [12,13]. These circumstances, some of which are unique to urinary symptoms, may introduce noise in the symptom incidence and shadow the potential dose–symptom relationships. Studies with longer follow-up may naturally accumulate more noise. These challenges in defining and appropriately analysing symptoms along with other potential methodological problems likely contribute to the elusiveness of a solid dose–symptom relationship [1,14].

In the realm of rectal dose–symptom studies, 'longitudinal' definition of toxicity has been proposed and found to be superior for certain endpoints [15,16]. Gulliford et al. [16] and Fiorino et al. [15] graded symptoms according to their persistence using variations of measures. The resulting improved dose–symptom

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relationships may be partly explained by the reduced noise. Alternatively, complete symptom information can be analysed using the multiple-event models [10,17] or the number of reported events can be analysed using the event-count models. To our knowledge, there are no previous urinary dose–symptom studies utilising these methods.

In this study, the bladder dose information and urinary symptom relationships were addressed using multiple-event and event-count models in addition to the more commonly utilised peak-symptom model. Data from patients accrued to the Trans-Tasman Radiation Oncology Group (TROG) 03.04 trial of Randomised Androgen Deprivation and RT (RADAR-NCT00193856) were utilised [18,19].

Materials and methods

Patients and treatments

The RADAR trial examined the influence of the duration of androgen deprivation with or without bisphosphonate treatment, adjuvant with radiotherapy [18,19]. Data collection, protocol requirements, treatment technique and quality assurance (QA) have been summarised previously [18–21]. 754 participants received external beam radiotherapy (EBRT) (without a brachytherapy boost) to either 66, 70 or 74 Gy and had complete bladder dose data collected, comprising a digital treatment plan export including axial computed tomography (CT) and associated planned dose matrix.

Bladder dose information

The digital RT treatment plan for every patient was independently reviewed and archived [22]. Bladder constraints were not applied and delineation of the bladder was not mandatory, thus, plans were reviewed and bladder outlining either verified or manually added. Centres were free to prescribe different bladder filling protocols; 701 patients were prescribed to full bladder, 34 empty and 19 with protocol unspecified. Physical doses to each voxel in the dose matrix for the bladder for each treatment phase were combined to generate EQD2 (equivalent dose in 2 Gy fractions using $\alpha/\beta = 6$ Gy [1,23]). Dose-surface information of the bladder wall (dose bin: 0.1 Gy) was calculated independently to ensure consistency across datasets submitted from different centres [24]. Cumulative bladder dose-surface histogram (DSH) data were derived from which the relative surface area of tissue receiving more than a threshold dose (R1 Gy, R2 Gy … R75 Gy) was calculated. Absolute DSH data for bladder has been suggested to be more robust to the impact of variable bladder filling in the high dose region [25]. As such, the absolute DSH for doses between 60 and 75 Gy (A60 Gy, A61 Gy … A75 Gy) were derived. The DSHs were also summarised using equivalent uniform dose (EUD) with exponent $a \in [1 \ldots 100]$ [26] (Supplementary material A).

Symptom measurement

Following treatment, patients were routinely followed up every 3 months for 18 months, then six-monthly up to 5 years and then annually. Atomised symptoms (dysuria, incontinence, frequency and haematuria) were considered using grades from physician-assessed LENT-SOMA [27] (Supplementary material B). Focusing on the late effect, only follow-ups at least 1 year after randomisation (i.e. 5 months after the end of EBRT) were considered.

Different data structures of the symptoms were used for the models (peak-symptom: binary, event-count: count, multiple-event: multiple binary) (Supplementary material C). For the peak-symptom models, an event was defined as the presence of symptoms at any time-point. For the event-count models, the total count of events accumulated was treated as the outcome. For the multiple-event model, observations were organised as one record per patient per follow-up creating multiple data points per patient. For the rest of this paper, abbreviations D_{P1}, D_{EC1} and D_{ME1} were used for peak-symptom, event-count and multiple-event models for grade $\geqslant 1$ dysuria, respectively. The numbers were changed to 2 for grade $\geqslant 2$. A similar convention was used for haematuria (H), incontinence (I) and frequency (F).

Multiple-event and event-count models

Generalised estimating equation (GEE), used in the multiple-event models, analyses longitudinal outcome data accounting all observations within a patient using a quasi-likelihood approach. The estimates from the GEE produce a measure of the impact of explanatory variables over all follow-ups simultaneously, reflecting the relationship to the longitudinal development of symptoms. Due to the existence of multiple observations per patient, robust standard errors and confidence intervals were estimated while accounting for the lack of independence [28]. To adjust for dependency of within-patient observations, an unstructured correlation matrix was specified allowing correlations to differ across follow-ups. The principles behind GEE are well described in Hanley et al. [28].

For event-count models, negative binomial (NB) regression was implemented where the number of events was regressed against the dose indices. The NB regression is an extension of the Poisson regression where the outcome of interest is a count [29]. Both NB and Poisson regressions are very similar but NB is less restrictive where equal distribution of the mean and variance of the count distribution is not assumed [30]. An introduction to NB and Poisson regression by Coxe et al. is recommended [29].

Statistical analysis

For peak-symptom models, associations were explored with logistic regression. Event-count and peak-symptom models were constructed as implemented in *MASS* (version 7.3-40) and multiple-event models using *geepack* (version 1.2-0) in R 3.1.2 (The R Foundation for Statistical Computing, Vienna, Austria) [31]. To obtain the least-biased estimate of the effect of dose on development of symptoms, adjustments were performed for clinical factors including baseline symptom grade and trial arm, which have previously been found to impact urinary symptoms [32,33]. To adjust for underestimation of peak symptoms and event counts for patients accrued at later dates, the number of available follow-ups was included as a covariate. Time from randomisation for each data point is inherent to multiple-event models. No robust common evaluation matrix is available for comparison across methods. Thus, the pattern of relationship between the dose indices and symptoms was discussed in terms of the odds ratios and p-values. For each endpoint-model combination, thresholds were derived from the most significant index, with the constraint that at least 10% of patients were on either side of the threshold. p-Values <0.05 were considered significant and p-values <0.20 to indicate suggestive association. Because of the correlated dose-surface information and the nature of this study which intentionally performed multiple analyses in a similar cohort, no correction for multiple comparisons was applied. Reporting all comparisons and allowing readers to draw conclusions has been considered a more practical option to application of a correction [34].

Results

The median number of late follow-up time-points was 10 (inter-quartile range; 7–11, median follow-up time; 60 months).