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Urinary bladder dose–response relationships for patient-reported genitourinary morbidity domains following prostate cancer radiotherapy

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ABSTRACT

Background and purpose: Radiotherapy (RT) induced genitourinary (GU) morbidity is typically assessed by physicians as single symptoms or aggregated scores including symptoms from various domains. Here we apply a method to group patient-reported GU symptoms after RT for localized prostate cancer based on their interplay, and study how these relate to urinary bladder dose.

Materials and methods: Data were taken from two Scandinavian studies ($N = 207/276$) including men treated with external-beam RT (EBRT) to 78/70 Gy (2 Gy/fraction; median time-to-follow-up: 3.6–6.4 y). Within and across cohorts, bladder dose–volume parameters were tested as predictors for GU symptom domains identified from two study-specific questionnaires (35 questions on frequency, incontinence, obstruction, pain, urgency, and sensory symptoms) using univariate and multivariate logistic regression analysis (MVA) with 10-fold cross-validation. Performance was evaluated using Area Under the Receiver Operating Characteristic Curve (A_z).

Results: For the identified *Incontinence* (2–5 symptoms), *Obstruction* (3–5 symptoms), and *Urgency* (2–7 symptoms) domains, MVA demonstrated that bladder doses close to the prescription doses were the strongest predictors for *Obstruction* (A_z: 0.53–0.57) and *Urgency* (A_z: 0.60). For *Obstruction*, performance increased for the across cohort analysis (A_z: 0.61–0.64).

Conclusions: Our identified patient-reported GU symptom domains suggest that high urinary bladder doses, and increased focus on both obstruction and urgency is likely to further add to the understanding of GU tract RT responses.

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State-of-the-art planning and delivery of radiotherapy (RT) for prostate cancer offers considerable opportunities to spare critical segments of the gastrointestinal tract. However, possibilities to spare genitourinary (GU) structures remain limited due to their critical locations relative to the prostate. Symptoms of the GU tract are commonly multi-faceted [1,2], and it is currently not fully understood how they relate to underlying dose–volume characteristics [3,4].

Commonly used toxicity scoring systems, *e.g.* the Common Terminology Criteria for Adverse Events (CTCAE) [5] capture a selected subset of GU symptoms, and are typically assessed by physicians. Patient-reported outcomes (PROs), reflecting an individual's experience of a certain symptom, have been advocated to capture GU and other symptoms difficult for an observer to quantify [3,4,6]. Typically, PROs result in an extensive amount of data, making it challenging to identify the most central symptoms [6]. To use PROs for quantitative RT dose–response modelling, it is crucial to understand the interplay between symptoms and to test that identified relationships are generalizable across studies and cohorts [7].

The purpose of this study was to explore whether RT dose of the urinary bladder relates to the occurrence and severity of patient-reported GU-specific symptom domains. Data on bladder dose and patient-reported GU symptoms were taken from two Scandinavian prostate cancer studies ($N = 483$). We used factor analysis to identify symptom domains, and univariate (UVA) followed by multivariate logistic regression analysis (MVA) to assess relationships between identified domains and bladder dose. Best-performing

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regression results were also further explored in predictive modelling of normal tissue response within and across cohorts.

Materials and methods

This computational exercise was performed with already collected data from two studies in Denmark (DK) and in Sweden (SW) [8,9], and included patients who had been treated with primary EBRT for localized prostate cancer. Information on the investigated cohorts and the study-specific questionnaires is summarized below; details can be found in previous publications [8–10].

Original study design and treatment

The DK study consisted of 212 patients who were treated at Aarhus University Hospital, Aarhus, in 2005–2007 [8]. The patients completed the Danish study-specific questionnaire in 2010 (median time to follow-up (range): 3.6 (2.4–5.0) years; average age (±SD): 70 ± 5.0 years; Table S1). The SW study consisted of 276 patients treated at the Sahlgrenska University Hospital, Gothenburg, in 1993–2006 [9,10]. The patients completed the Swedish study-specific questionnaire in 2008 (median time to follow-up: 6.4 (1.2–14) years; average age: 64 ± 5.0 years). In this work we focus on the 12 DK and 23 SW questions that directly reflected physical symptoms of potentially RT-related GU injuries: urinary frequency, incontinence, obstruction, pain, urgency, and sensory symptoms (Table S2). Methodological descriptions of the design (including validation) of the two PROs can be found in [11–13].

Primary EBRT had been planned based on CT imaging and was planned and delivered with the patient in supine position and prescribed according to the International Commission on Radiation Units and Measurements recommendations [14]. The majority of patients received conformal three- or five-field treatments with 15 MV photon beam quality and the total dose was 78 Gy in DK and 70 Gy in SW. The treatment had been delivered in 2 Gy fractions (five fractions/week). For DK patients, the planning target volume (PTV) margin was 7 mm in all directions, except craniocaudally where it was 9 mm, and the majority had been treated with a two-phase approach including the proximal seminal vesicles to 50 Gy in the first phase. For SW patients, the PTV margin was 20 mm in all directions, except posteriorly where the margin was the lesser of 15 mm or half of the rectal cross-sectional area. No bladder preparation protocol (including bladder filling instructions) was applied. All patients were treated according to the clinical routines in use at the respective hospital during the studied time period. Individual dose–volume histograms (DVHs) were electronically available and extracted from the planned 3D bladder dose distributions. The bladder had been consistently delineated from the apex to the fundus for each patient under supervision of a senior Radiation Oncologist. The following DVH-based parameters were studied as candidate predictors for the identified GU symptom domains (see preceding section below): the relative volume receiving x Gy, V_x (V_5–V_{80} and V_5–V_{75} for DK and SW, respectively, in steps of 5 Gy [%]), the minimum dose to the hottest x%, D_x, (D_5–D_{100}, in steps of 5% [Gy]), the mean dose of the hottest x% volume, MOH_x (MOH_5–MOH_{100}, in steps of 5% [Gy]), and the maximum and the mean dose (D_{max} and D_{mean}, respectively).

Symptom domains and dose–response outcome variables

Given the level of detail in the two PROs and to avoid subjective grouping of symptoms from various GU-specific symptom domains, factor analysis was applied to the 12 and 23 questions of potentially RT-related GU injuries in DK and SW, respectively [15]. Factor analysis is a statistical method to investigate the relationship between items in a dataset (Appendix). Dose–response outcome variables for each symptom domain were then defined as the resulting binary response when addressing the presence of any individual symptom (Boolean 'OR condition' used when combining symptoms). To focus on clinically relevant and likely RT-induced symptoms, a moderate symptom severity (defined in dialogues with M.H and D.A, with at least weekly/50% of the times occurrence; Tables 1 and S2), and a symptom prevalence $\geqslant$5% were considered.

Statistics

To identify DVH-based predictors, logistic regression with UVA followed by MVA was applied. A candidate predictor was suggested by a two-sided p-value < 0.10 on UVA, and a Pearson's correlation coefficient (P_r) < 0.85 with any other selected candidate predictor. Best-performing domain-specific symptoms were then investigated in a normal tissue complication probability setting. To investigate model generalizability across cohorts, dose–response modelling was performed in the joint DK and SW dataset for the combination of symptoms of specific domains with the highest predictability within each cohort. All analyses were performed in MATLAB v.R2013a.

Regression analyses

In addition to the DVH-based parameters, seven patient-specific parameters were investigated: age at RT (continuous [y]), bladder volume (continuous [cm^3]), diabetes (binary; yes = 9%/12% in DK/SW], hormonal treatment (anti-androgens/gonadotropin-releasing hormone/orchiectomy; binary; yes = 91%/16% in DK/SW), intensity-modulated RT (binary; yes = 6% in DK), current (2)/-former (1)/no (0) smoker (categorical; 2 = 69%/60% in DK/SW), and time to follow-up (continuous [y]; Table S2). The same criteria as used for the DVH-based candidate predictors regarding p-value < 0.10 and P_r < 0.85, was also applied to the patient-specific parameters. To investigate model generalizability, both the UVA and MVA were performed using 10-fold cross-validation by 50 iterations, resulting in a total of 500 generated models. In addition to a combined backward-stepwise MVA approach ($MVA_{stepwise}$), a Least Absolute Shrinkage and Selection Operator approach [16] (MVA_{LASSO}) was considered a Supplementary method to find the predictors from the set of UVA-suggested candidate predictors. MVA model performance was evaluated based on the area under the receiver-operating curve (A_z), assessed as the mean over the 500 generated models. Important DVH-based predictors were identified as occurring in at least 25 of the 500 generated models *i.e.* having a frequency >5%. Added model predictability, as measured from an increase in A_z, determined if any of the patient-specific parameters to be included into the final models.

Normal tissue complication probability modelling

The Lyman-Kutcher-Burman (LKB) model [17–19] was used for dose–response modelling. Data were fitted using a Maximum Likelihood method in a grid search approach (a range: 0.001:100 in 56 steps, D_{50} range: 50:150 in 101 steps, and m range: 0.01:1.1 in 55 steps) with the Profile Likelihood method to calculate 95% confidence intervals (CIs).

Results

Dose–response modelling within cohorts

The identified symptom domains (No. of symptoms) for DK consisted of *Incontinence* (3), *Obstruction* (5), and *Urgency* (7; Fig. S1), of which symptoms of the two latter domains qualified for dose–response modelling since the prevalence was $\geqslant$5% for the majority