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Original Research Article

# A case-control study using motion-inclusive spatial dose-volume metrics to account for genito-urinary toxicity following high-precision radiotherapy for prostate cancer☆

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ABSTRACT

*Background and purpose:* The risk of genitourinary (GU) toxicity is dose-limiting in radiotherapy (RT) for prostate cancer. This study investigated whether motion-inclusive spatial dose/volume metrics explain the GU toxicity manifesting after high-precision RT for prostate cancer.

*Material and methods:* A matched case-control was performed within a cohort of 258 prostate cancer patients treated with daily cone-beam CT (CBCT)-guided RT (prescription doses of 77.4–81.0 Gy). Twenty-seven patients (10.5%) presented late RTOG GU ≥ Grade 2 toxicity and those without symptoms of toxicity prior treatment (N = 7) were selected as cases. Each case was matched with three controls based on pre-treatment GU symptoms, age, Gleason score, follow-up time, and hormone therapy. Thirteen CBCTs per patient were rigidly registered to the planning CT using the recorded treatment shifts, and the bladder was manually contoured on each CBCT. Planned and actually delivered dose/volume metrics (the latter averaged across the CBCTs) were extracted from the bladder and its subsectors, and compared between cases and controls (two-way ANOVA test).

*Results:* There were no significant differences between planned and delivered dose/volume metrics; also, there were no significant differences between cases and controls at any dose level, neither for planned nor delivered doses. The cases tended to have larger bladder volumes during treatment than controls (221 ± 71 $cm^3$ vs 166 ± 73 $cm^3$; p = 0.09).

*Conclusions:* High-precision RT for prostate cancer eliminates differences between planned and delivered dose distributions. Neither planned nor delivered bladder dose/volume metrics were associated to the remaining low risk of developing GU toxicity after high-precision radiotherapy for prostate cancer.

## 1. Introduction

Modern high-precision external-beam radiotherapy (RT) for prostate cancer enables dose escalation to the prostate gland by using resource-intensive protocols, including daily image-guided RT (IGRT) [1], monitoring of bladder and rectum filling status [2,3], and narrow margins [1,4]. These protocols have improved clinical outcomes including overall survival [5,6]. However, the risk of genitourinary (GU) toxicity, which compromises patient's quality of life [7–9], still has to be balanced against the risk of local failure, owing to the close proximity between the bladder and the prostate. GU toxicities represent the dominating domain of late normal tissue effects (also gastro-intestinal toxicity affects patients, but at a much lower level), being the primary dose-limiting factor in conventional fractionated high-precision RT for prostate cancer [5].

Early pre-IGRT era studies reported that bladder volumes receiving intermediate to high doses as seen in the planning CT were only moderately associated with the risk of GU toxicity (AUC = 0.74–0.78)

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[10,11]. It was therefore suggested that planned dose-volume histograms (DVHs) are not representative of the dose being delivered [12]. The introduction of IGRT, and in particular the use of daily cone beam CT (CBCT)-based set-up verification, confirmed large variations in bladder volume throughout the RT course and the consequential variations in dose distributions [13–15]. Additionally, differences in motion and deformation patterns among bladder subsectors were observed, with the inferior part being less affected by changes in bladder filling [16,17]. In particular, the inferior sector is in close proximity to the prostate, and typically receives doses up to the prescription level [13]. Recently, it has been demonstrated that high doses delivered to the trigone/bladder neck may drive the development of late GU toxicity [18–20], suggesting spatial effects in GU dose-response relationships. These methods require however additional computations or delineations during the RT planning process compared to a full bladder DVH-based analysis. The aim of this study was therefore to explore whether delivered spatial bladder DVHs explain the occurrence of GU toxicity after RT for prostate cancer. The analysis was conducted within a matched case-control approach and the delivered DVHs were derived from daily CBCT-based IGRT.

## 2. Material and methods

### 2.1. Patient cohort and treatment

A total of 449 patients were treated with external-beam RT for prostate cancer at the University of California, San Diego, between 2008 and 2014. Of these patients, 258 patients were treated with daily CBCT guidance with the remainder being kV imaging to fiducial markers or some combination of kV and CBCT. Within this group 27 patients (10.5%) had ≥Grade 2 late GU toxicity according to the Radiation Therapy Oncology Group (RTOG) criteria [21]. For case selection additional inclusion/exclusion criteria were applied and only patients with clear new onset grade 2 GU toxicity post-RT without prior symptoms were included as cases, for example hematuria requiring bladder irrigation, new obstruction requiring dilation, etc. Patients with subjectively graded toxicities (e.g. mild for grade 1, moderate for grade 2) or patients with some level of urinary frequency prior to treatment or unclear baseline urinary function receiving alpha blockers were excluded from further analysis. Finally, there were eight patients with grade 2 toxicity that were without subjective assessment or any pre-treatment level of dysfunction in the area of interest were selected as cases. The remaining patients presenting with Grade 0 late GU toxicity and non pre-existing significant GU symptoms were considered potential candidates for controls. For each case three controls were matched according to age (± five years), Gleason score, pre-treatment GU status, follow-up time and use of neoadjuvant androgen deprivation therapy. For one of the cases it was not possible to find matched controls fulfilling the matching criteria, and seven cases were finally included in the study (total of 28 patients, cases and controls). Each case and the matched controls received the same treatment regimen, dose prescription and fractionation schedule; where three cases received pelvic irradiation and four cases local treatment. If a case presented more than three potential controls, the selected controls were those presenting the smallest difference in the follow-up time. The collection of the toxicity information and the classification of the patient status were performed by the responsible medical doctor (AH), who was present in all the visits of the patients related to problems following treatment. The follow-up time (mean ± SD) for the cases was 3.1 ± 1.3 years, whereas for the controls was 3.2 ± 1.3 years.

The patients were prescribed to total doses of 79.2–81.0 Gy (in 43–45 fractions), delivered to the intact prostate in two treatment options: either local treatment to the prostate and seminal vesicles or pelvic node irradiation, followed by a boost to the prostate and seminal vesicles. All patients underwent planning CT scanning and all daily treatments in supine position with the lower extremities immobilized in a VacLock device (Civco Radiotherapy, Coralville, IA). Planning target volumes (PTVs) were generated in the planning CT using margins of 3 mm posteriorly and 7 mm in all other directions from the clinical target volumes (CTVs). All treatment plans were performed in Eclipse v.8–10 (Varian Medical Systems, Palo Alto, CA, USA), with the dose to the bladder restricted to $V_{80Gy} < 15\%$, $V_{75Gy} < 25\%$, $V_{70\%} < 35\%$ and $V_{65Gy} < 50\%$ according to the QUANTEC recommendation [13]. All patients included in the study received intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT) in combination with a strict full bladder/empty rectum protocol. More information on the utilized treatments modalities can be found in Casares-Magaz et al. [22].

### 2.2. Registration and Contouring

For each patient, thirteen CBCTs (all daily scans from the first week of treatment, and then weekly) were rigidly registered to the planning CT and connected dose matrix using the clinically recorded 3D treatment shifts (only translations). Dose distributions at each CBCTs were a copy of the dose matrix at the planning CT, assuming that variations in dose distributions are negligible due to the interfractional changes in the patient's anatomy under strict full bladder and empty rectum protocol. This assumption has been confirmed in a previous study from our group where dose distributions were recalculated on set of worst-case scenarios with respect to varying anatomies, where only differences up to 2% were observed [23]; similar findings were reported by Sharma et al. using a larger cohort of patients [24].

On each CBCT the bladder was manually contoured, and contours were reviewed and approved by the responsible radiation oncologist. The bladder shell was extracted for each of the registered CBCT using a 3 mm inner margin, and then bladder shell halves and quadrants were created using two orthogonal planes (axial and coronal) drawn through the center of mass of each bladder. A total of ten structure definitions were investigated: whole bladder, bladder shell, anterior, posterior, superior, inferior, anterior/superior, anterior/inferior, posterior/superior, posterior/inferior. Contouring, registration and extraction of bladder shells and substructures were performed in MIM Maestro v.6.5.4 (Mim Software Inc., Cleveland, OH, USA) following our previously used workflow [22].

### 2.3. Statistical analysis

For each patient, bladder volume and DVH metrics (absolute and relative $V_{5\%}$–$V_{105\%}$ in 5% steps) were extracted for the planning CT, for each registered CBCT, and for all segmented structures. DVH metrics were compared between cases and controls using two-way ANOVA test accounting for the matching information. For the analysis of the delivered dose/volume metrics the weighted average was used, where the weight was equal to the number of fractions applied to each CBCT (one for daily CBCTs from the first week, and five for the weekly CBCTs from the following weeks). The statistical analysis was performed in Stata 13.1 (StataCorp, College Station, TX, USA) and in Matlab R2017b (The MathWorks Inc., Natick, MA, USA).

## 3. Results

### 3.1. Spatial DVH metrics for cases vs. controls

Absolute volume DVH metrics of the bladder and the bladder shell subsectors were similar between cases and controls (two-way ANOVA) for both the planned ($p > 0.26$) and the delivered ($p > 0.57$) dose distributions (Fig. 1). However, spatial DVH metrics captured differences between cases and controls in dose re-distribution patterns across the bladder sectors. Inferior and anterior/inferior sectors had slightly higher delivered metrics for cases (p-value > 0.07), although overall, controls had slightly higher delivered DVH metrics for the bladder shell.