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Dose to the Bladder Neck Is the Most Important Predictor for Acute and Late Toxicity After Low-Dose-Rate Prostate Brachytherapy: Implications for Establishing New Dose Constraints for Treatment Planning

Lara Hathout, MD*, Michael R. Folkert, MD*, Marisa A. Kollmeier, MD*, Yoshiya Yamada, MD*, Gil'ad N. Cohen, MS†, and Michael J. Zelefsky, MD*

*Departments of Radiation Oncology, New York, New York

†Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, New York

Abstract

Purpose—To identify an anatomic structure predictive for acute (AUT) and late (LUT) urinary toxicity in patients with prostate cancer treated with low-dose-rate brachytherapy (LDR) with or without external beam radiation therapy (EBRT).

Materials and Methods—From 7/2002 to 1/2013, 927 patients with prostate cancer (median age, 66) underwent LDR brachytherapy using I-125 (n=753) or Pd-103 (n=174) as definitive treatment (n=478) and as a boost (n=449) followed by supplemental EBRT (median dose, 50.4 Gy). Structures contoured on Day 0 postimplant CT scan included prostate, urethra, bladder, and the bladder neck, defined as 5 mm around the urethra between the catheter balloon and the prostatic urethra. AUT and LUT were assessed using CTCAE v 4. Clinical and dosimetric factors associated with AUT and LUT were analyzed using Cox regression and receiver-operating characteristic analysis to calculate area under the receiver operator curve (ROC) (AUC).

Results—Grade 2 AUT and grade 2 LUT occurred in 520 (56%) patients and 154 (20%) patients, respectively. No grade 4 toxicities were observed. Bladder neck D2cc retained significant association with AUT (hazard ratio [HR], 1.03; 95% CI, 1.03–1.04) ($P<.0001$) and LUT (HR, 1.01; 95% CI, 1.00–1.03) ($P=.014$) on multivariable analysis. When comparing bladder neck with the standard dosimetric variables using ROC analysis (prostate V100>90%, D90>100%, V150>60%, urethra D20>130%), bladder neck D2cc>50% was shown to have the strongest prognostic power for AUT (AUC, 0.697; $P<.0001$) and LUT (AUC, 0.620; $P<.001$).

Reprint requests to: Michael J. Zelefsky, MD, Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, Box 22, New York, NY 10065. Tel: (212) 639-6802; Fax: (212) 639-8876; zelefsm@mskcc.org.

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Conflicts of interest: none.

Conclusions—Bladder neck D2cc>50% was the strongest predictor for grade 2 AUT and LUT in patients treated with LDR brachytherapy. These data support inclusion of bladder neck constraints into brachytherapy planning to decrease urinary toxicity.

Introduction

Low-dose-rate (LDR) brachytherapy with permanent seed implantation with or without supplemental external beam radiotherapy (EBRT) is an effective and well-tolerated treatment for patients with clinically localized prostate cancer. Whether brachytherapy is used as definitive treatment or as a boost followed by supplemental EBRT, it is associated with excellent local control and biochemical disease-free survival outcomes [1–6]. Brachytherapy offers the advantage of intra-prostatic dose escalation at dose levels, which could not be safely administered with external beam radiotherapy alone. Additionally, intraoperative urethra-sparing approaches using strict dosimetric constraints provide opportunities for limiting the dose to the urethra to reduce urinary toxicity and the risk of urethral strictures [7–9]. The American Brachytherapy Society (ABS) recommends the application of dose constraints for the urethra when using permanent seed implantation, including maintaining a urethra V5<150% and urethra V30<125% [10]. However, the most critical anatomic structure associated with post-radiotherapy urinary toxicity is not well established. Retrospective reports have drawn associations between various factors such as urethral dose, prostate volume, baseline International Prostate Symptom Scores (IPSS), use of neoadjuvant androgen-deprivation therapy (ADT), and greater number of needles implanted with increased risk of significant acute urinary toxicity [11]. Several small retrospective reports have investigated the correlation of urinary toxicity with the dose to the lower urinary tract segments [12] and found an association between the dose to the urethral base/bladder neck and urinary toxicity [13, 14]. We previously reported a strong association between the dose to the bladder neck/trigone and long-term urinary function in patients treated with EBRT for prostate cancer [15].

We conducted the present study to validate the importance of the bladder neck dose as a predictor for acute and late urinary toxicity in a large cohort of patients treated with LDR seed implantation of the prostate as definitive therapy or as a boost followed by supplemental EBRT for prostate cancer.

Materials and Methods

Patient and treatment characteristics

Before conducting this retrospective study, Institutional Review Board approval was obtained. From 7/2002 to 1/2013, 927 consecutive patients with a median age at diagnosis of 66 years (interquartile range [IQR], 60–71) were treated at our institution, with a median follow-up of 42.5 months (IQR, 28–61) and a minimum follow-up of 12 months. Patients with low-risk or favorable intermediate-risk prostate cancer as defined by Zumsteg et al [16] (n=478) were treated with LDR brachytherapy alone. Patients with unfavorable intermediate risk or high risk (n=449) received a combination of LDR brachytherapy followed by supplemental EBRT. The majority of patients had low- and intermediate-risk prostate cancer as per the NCCN risk classification, with only 7.4% of patients having high-risk disease

(n=69). All patients had confirmation of their diagnosis with biopsy review by a urological pathologist at our institution prior to treatment. Magnetic resonance imaging (MRI) was obtained prior to treatment in 92% of patients; MRI imaging was not required for treatment, and reasons for not obtaining an MRI included patient refusal and inability to undergo MRI imaging due to pacemaker/defibrillator or other implant placement.

Short-course ADT was administered to 249 patients (27%) for a maximum of 6 months and routinely discontinued after the end of the LDR procedure or EBRT. In general, patients with large gland size ($>50 \text{ cm}^3$) were treated with 3 months neoadjuvant ADT for cytoreduction prior to brachytherapy. Definitive brachytherapy was delivered to 478 patients (51.6%) using Iodine-125 seeds to a total dose of 144 Gy. Brachytherapy delivered as a boost followed by EBRT was delivered to 449 patients (48.4%) using Pd-103 (100 Gy) and I-125 (110 Gy) seeds. Patients treated with combined therapy received supplemental EBRT to the prostate and seminal vesicles to a median dose of 50.4 Gy (range, 45–50.4 Gy). The median baseline IPS score was 5 (range, 3–9). Patient characteristics are provided in Table 1.

Study design

This retrospective study was conducted to assess and compare clinical, anatomic, and dosimetric predictors of acute and late urinary toxicity following LDR permanent brachytherapy seed implantation as definitive treatment or as a boost followed by EBRT.

Clinical variables including the patient's age, medical comorbidities including diabetes and smoking habits, use of phosphodiesterase type 5 inhibitor, baseline International Prostate Symptom Score (IPSS), use of neoadjuvant ADT, baseline urinary medications and pretreatment prostate volume on MRI were assessed.

Contours of the prostate, urethra, bladder and rectum were drawn on the day 0 CT scan shortly after the procedure and thus prospectively recorded; delineation of the urethra was facilitated by insertion of a catheter. The Foley catheter was firmly tugged into place before acquiring the CT scan. The bladder neck was retrospectively contoured on all day 0 CT scans by a blinded observer to the primary endpoint and reviewed by a second blinded reviewer. The bladder neck volume was defined as 5 mm around the Foley catheter-defined urethra on the CT slices between the catheter balloon and the prostatic urethra to a minimum volume of 2 cm^3 (mean, 2.2 cm^3) as shown in Fig. 1. As the bladder neck contour is highly objective, based on strict anatomic guidelines (standard 5 mm expansion around the Foley-defined urethra immediately inferior to the easily-visualized Foley balloon), these contours are very consistent, with volume standard deviation of only 0.21 cm^3 (less than 10%). The following dosimetric parameters were reported and analyzed: prostate V100, D90 and V150, urethra D20, D5 and D1cc, bladder V100, D2 and D1cc and bladder neck V100, D2 and D1cc (see supplementary Table 1). In addition, the homogeneity index (HI), defined as $\text{HI} = [(\text{Prostate V100} - \text{Prostate V150}) / \text{Prostate V100}]$, was calculated and assessed.

Brachytherapy technique

The LDR seed implantation procedure and intraoperative planning technique used in this study have been previously described in detail [8]. Briefly, the patients are intubated under general anesthesia, with intravenous dexamethasone (8 mg) given at time of induction.

Interstitial needles were inserted into the peripheral substance of the prostate gland through a perineal template under sagittal and axial transrectal ultrasound image guidance. Transurethral aerated gel was applied to maximize urethral visualization, and axial ultrasound images of the prostate were subsequently acquired at 5 mm increments from the base of the prostate to the apex and transferred into the brachytherapy treatment-planning system. Contours of the target volume and organs at risk were drawn on each axial image for computer-based three-dimensional reconstruction. Needle positions were identified and reconstructed using template coordinates. An inverse-planning system employing a genetic optimization algorithm for intraoperative ultrasound-guided transperineal technique was used. A conformal treatment plan and associated seed-loading pattern with respect to the predetermined dose-volume constraints (prostate V100>90%, prostate D90>100%, maximal urethral dose <130%, and average rectal dose <80% of the prescription dose) was generated. Radioactive seeds were placed using a Mick applicator (Mick Radio-Nuclear Instruments, Inc., Mount Vernon NY, USA) under ultrasound and fluoroscopic image guidance according to the approved treatment plan. A Day 0 post-implant CT scan at 3 mm intervals was obtained 4 hours after the procedure with a Foley catheter in place for the majority of patients from 2002 to 2010. Since 2010, a portable CT-fluoroscopic unit was used to obtain real-time kilovoltage cone-beam CT images with the patient in the supine position immediately after the procedure and prior to anesthesia reversal.

In all cases, the urinary catheter was removed in the post-anesthesia recovery room, and patients were discharged with a prescription for tamsulosin successful voiding trial.

Outcome measurement

The patients' IPSSs were obtained prior to the brachytherapy procedure and repeated at each follow-up. Patients were evaluated every 3 months for the first year, every 6 months for the next 5 years, and yearly thereafter. At baseline and at each subsequent visit, the urinary toxicity was recorded and assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v.4. Acute urinary toxicity (AUT) was defined as urinary toxicity occurring within 12 months of LDR implant. Late urinary toxicity (LUT) was defined as urinary toxicity occurring more than 12 months after the LDR implant. Urinary symptom resolution was defined as a return of the total IPSS to within 5 points of the baseline score.

Statistical analysis

Frequencies and percentages were used for categorical variables, and medians and interquartile ranges were used for continuous variables. Kaplan-Meier survival curves were used to calculate the time to IPSS resolution; comparison of outcomes based on risk factors was performed by log rank test. Factors associated with AUT were identified using Cox proportional hazards regression techniques and hazard ratios (HR) were calculated. Receiver-operating characteristic analysis was performed to calculate area under the receiver operator curve (ROC) (AUC) to compare strength of predictors for AUT and LUT. $P<.05$ was considered statistically significant.

Multivariable models were developed incorporating factors with threshold P values $\leq .1$ on univariate analysis. For factors with a high likelihood of interaction (ie, prostate V100 vs.

D90, prostate V150 vs. HI, etc.), the factors with the largest HR on univariate analysis were included. Statistical analysis was performed using IBM SPSS v.21 (SPSS Inc., Chicago, IL).

Results

Acute grade 2 and grade 3 urinary toxicity occurred in 519 (55.9%) and 1 (0.1%) patients, respectively. No acute grade 4 toxicity was observed in this cohort.

On univariate analysis, prostate volume on pretreatment MRI ($P<.0001$), prostate D90 ($P=.02$), bladder V100 ($P<.0001$), bladder D2cc ($P<.0001$), bladder D1cc ($P<.0001$), bladder neck D2cc ($P<.0001$), bladder neck D1cc ($P<.0001$), the number of implanted needles ($P<.0001$) and seeds ($P<.0001$), and brachytherapy as definitive treatment vs. combined treatment ($P<.0001$) were associated with grade 2 AUT as shown in Table 2. Age, smoking habits, isotope, diabetes, use of neoadjuvant ADT, urethra D20, D5 and D1cc. and baseline IPSS were not associated with AUT.

On multivariate analysis, bladder neck D2cc (HR, 1.03; 95% CI, 1.03–1.04) ($P<.0001$), and brachytherapy as definitive treatment (HR, 1.3; 95% CI, 1.08–1.63) ($P=.01$) retained significant association with AUT, as shown in Table 2. When comparing the bladder neck D2cc>50% with the other published dosimetric constraints using ROC analysis (prostate V100>90%, D90>100%, V150>60%, urethra D20>130%), bladder neck D2cc>50% (AUC 0.697, $P<.0001$) was shown to have the strongest prognostic power for AUT (Table 3).

Late grade 2 and grade 3 urinary toxicity occurred in 154 (17%) and 31 (3%) patients, respectively. No late grade 4 toxicity was observed. On univariate analysis, prostate volume on pretreatment MRI ($P=.004$), prostate V100 ($P=.01$), prostate D90 ($P<.0001$), prostate V150 ($P=.001$), bladder V100 ($P<.0001$), bladder D2cc ($P<.0001$), bladder D1cc ($P<.0001$), bladder neck D2cc ($P<.0001$), bladder neck D1cc ($P<.0001$), HI ($P=.002$), and number of implanted needles ($P<.0001$) were associated with LUT.

On multivariate analysis, bladder neck D2cc (HR, 1.02; 95% CI, 1.00–1.03 ($P=0.014$), the homogeneity index (HR, 0.16; 95% CI, 0.03–0.9) ($P=.04$) and the number of implanted needles (HR, 1.09; 95% CI, 1.02–1.16) ($P=.012$) retained significant association with LUT (Table 4). The bladder neck D2cc>50% (AUC, 0.620; $P<.0001$) was the strongest predictor for LUT using ROC analysis (Table 3), compared to other published dosimetric constraints.

Urinary symptom resolution was achieved in 847 patients (91.4%); 80 patients (8.6%) did not reach return to baseline IPSS. The median time to IPSS resolution was 18 months (IQR, 9.8–39.4). Patients with bladder neck D2cc <50% had a significant quicker median time to urinary symptom resolution on log rank test as shown in Fig. 2. Indeed, median time to IPSS resolution in patients with bladder neck D2cc >50% was 23.6 months (95% CI 20.7–26.5) vs. 17.6 months (95% CI 15.5–19.7).

Discussion

Our findings provide strong evidence that the bladder neck may represent the critical anatomic subunit associated with post-radiotherapy urinary-related toxicity. Indeed, the

bladder trigone appears to be responsible for micturition by contracting during bladder filling, helping to keep the ureteral orifices open and the bladder neck shut [17], and injury or irritation of this structure may affect continence or urinary retention. Our present study represents an extension of a previous report where we demonstrated that, among patients treated with IGRT alone, the dose to the bladder neck/trigone is strongly associated with urinary toxicity [15]. We conducted this present study to assess the impact of the dose to the bladder neck on urinary toxicity in patients treated with a LDR brachytherapy as definitive treatment or in conjunction with EBRT. Our study supports the correlation between dose to the bladder neck and the incidence of grade 2 AUT and LUT. For every increase in the bladder neck D2cc dose of 1%, there is a 3% and 2% increase in the risk of acute and late urinary toxicity, respectively. Bladder neck D2cc (HR, 1.03; 95% CI, 1.03–1.04; $P<.0001$) retained significance as an independent predictive factor for AUT on multivariate analysis, and bladder neck D2cc >50% was the strongest predictor of AUT on ROC analysis with AUC=.697 ($P<.0001$); other previously published factors were little better than random chance. As for LUT, bladder neck D2cc (HR, 1.02; 95% CI, 1.00–1.03; $P=.014$) was significantly correlated with LUT on multivariable analysis, and the bladder neck D2cc>50% (AUC, 0.620; $P<.0001$) was the strongest predictor for LUT using ROC analysis, with other published factors again serving no better than random chance.

AUT is frequent after permanent prostate LDR brachytherapy; intensity of symptoms usually peaks 1 to 3 months following the brachytherapy procedure and returns to baseline after approximately 12 months [18–20]. Keyes et al. have reported a shorter time to resolution of elevated post-treatment IPSS in patients with higher baseline IPSS [11]. In addition, higher prostate D90, maximum post-implant IPSS, and urinary retention have been proposed as predictors for acute urinary toxicity [11]. Several prior studies have found a correlation between the dose to the urethra and urinary toxicity and urethral strictures [7, 8, 21], while other studies do not support this finding [9, 22, 23]. While the ABS has established conservative urethral dose constraints for the urethra, there does not seem to be a clear threshold dose for the urethra that reliably predicts for urinary toxicity. No dose constraints have been firmly established for the bladder, in whole or in part [10, 24]. To our knowledge, this is the first study to report a correlation between bladder neck D2cc and both AUT and LUT.

A recent study by Hsu et al. reported a negative association between HI and acute genitourinary adverse events in patients treated with a combination of external beam radiation therapy and high-dose-rate brachytherapy [25]. In our present study, a lower HI was correlated with a higher rate of LUT (HR, 0.16; 95% CI, 0.03–0.9) ($P=.04$) in patients treated with LDR, although it was not associated with AUT. Prostate V150 is often used to evaluate the homogeneity of the implant and correlates with urethral strictures. The ratio of prostate (V100–V150)/V100 is a good indicator of hot spots within the target volume, and increasing the HI could potentially decrease LUT. As yet, there is no HI threshold established in the literature.

Supplemental EBRT was significantly correlated with a lower incidence of AUT in our study, suggesting that acute urinary toxicity might be more dependent on the brachytherapy dose delivered than EBRT. Previous studies have reported a lower rate of urinary retention

with brachytherapy and supplemental EBRT was vs. brachytherapy alone [26–28], which is in agreement with our findings.

The choice of isotope did not have an impact on AUT or LUT. Our present study is in agreement with a previous study from our institution comparing I-125 and Pd-103, which did not reveal any difference in terms of toxicity and biochemical outcome between the two isotopes [29].

Prior studies have suggested a correlation between the different urethral segments/bladder and urinary toxicity for patients treated with LDR brachytherapy [20, 30, 31]. Higher urethral dose at the prostate base, larger prostate volume, and larger number of needles were associated with a higher maximum IPSS during the first year after the implant, suggesting the importance of outlining the urethral base [14]. Steggerda et al. [13] proposed bladder neck D0.5cc >175 Gy (120.7%) of the prescription dose as a potential dose constraint for patients treated with I-125 definitive brachytherapy. The authors did not specify the mean bladder neck volume contoured. The D0.5cc corresponds most probably to the maximum dose received by the bladder neck, which in our study would be close to the D2cc since the minimum bladder neck volume contoured was 2 cm³.

The major strengths of our study are the large number of patients, the consistent delineation of the bladder neck structure on day 0 post-implant CT scan, and the inclusion of previously identified relevant clinical and dosimetric parameters in our analysis. Delineation of the bladder neck as performed in this study is reproducible, as this landmark is easily identifiable on CT scan when a Foley catheter is in place and closely approximates the true location of the bladder neck, which is otherwise only well visualized on MRI. It is contoured on the day 0 (intraoperative) CT scan, which avoids unnecessary catheterization on the day 30 post-implant CT scan.

The constraint of bladder neck D2cc < 50% as described in this study has the advantage of being easily applicable for both I-125 and Pd-103 isotopes and for patients treated with either brachytherapy alone or brachytherapy followed by supplemental external beam radiotherapy. In addition, the bladder neck constraint could be easily integrated in the ultrasound-based intraoperative planning by limiting the D2cc to 50% or less of the prescription dose. Limiting the bladder neck D2cc to 50% did not affect the implant quality; all dosimetric criteria were respected.

While this study does support the definition of a new dosimetric constraint for the bladder neck, there are nonetheless several limitations. Foremost are the inherent biases associated with any retrospective study; treatment with brachytherapy is predicated in part on both patient and physician perceptions, and patient-reported symptoms reported prior to treatment can influence whether the patient would be treated with brachytherapy at all, as well as how the implant is designed at the time of treatment by the physician. In addition, physicians themselves can be inconsistent with regards to the scoring of urinary toxicity.

Conclusions

Bladder neck D2cc>50% was identified as a strong predictor for acute and late urinary toxicity in patients treated with LDR brachytherapy with and without supplemental EBRT. These data support the potential benefit for inclusion of bladder neck constraints into brachytherapy treatment planning, as constraining the dose to this region may decrease urinary-related symptoms after treatment. Our findings will require further studies to validate. A prospective study is presently underway at our institution to assess the validity of the proposed bladder neck dose constraint.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SUMMARY

We conducted a retrospective study to determine the strongest predictor for urinary toxicity for patients treated with interstitial prostate seed implantation. Dose to the bladder neck was the strongest predictor for acute and late urinary toxicity compared to the standard dosimetric variables. This data supports the inclusion of bladder neck constraints into brachytherapy treatment planning, as constraining the dose to this region may decrease urinary-related symptoms after treatment.

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Fig. 1.
Contour of bladder neck on day 0 post-implant CT scan.

Fig. 2.
Kaplan Meier survival curves: time to IPSS resolution according to the bladder neck D2cc dose 1

Table 1

Baseline clinical characteristics of all patients

Characteristics	Total, N (%)
Median age (IQR)	66 (61–70)
Tumor stage	
T1c, T2a	820 (88.4%)
T2b-T2c	85 (9.2%)
T3a-T3b-T3c	21 (2.3%)
T4	1 (0.1%)
Gleason score	
6	458 (49.4%)
7	405 (43.6%)
8-9	64 (7%)
Pre-treatment PSA	
Median (IQR)	5.5 (4.3-7.7)
EBRT dose (cGy)	
Median (range)	5040 (4140-5040)
Comorbidities	
Diabetes	49 (11%)
Current smoker	34 (8%)
Former smoker	198 (44%)
Never smoker	184 (41%)
Unknown	33 (7%)
Use of PDE-5I at time of diagnosis	196 (21%)
Neoadjuvant ADT	249 (27%)
Isotope used	
Iodine- 125 (definitive dose, 144Gy)	478 (51.6%)
Iodine-125 (boost, 110 Gy)	275 (29.6%)
Palladium-103 (boost, 100 Gy)	174 (18.8 %)
Baseline IPSS	
Median (IQR)	5 (3-9)
Pretreatment MRI prostate volume (cm ³)	33 (26-45)
Median (IQR)	
Follow up, months	2
Median (IQR)	42.5 (28-61)

Abbreviations: ADT = androgen-deprivation therapy; EBRT = external beam radiotherapy; IPSS = International Prostate Symptom Score; IQR = interquartile range; PDE-5I = phosphodiesterase type 5 inhibitor.

Table 2

Univariate and multivariate analysis for acute urinary toxicity

	Univariate		Multivariate	
	<i>P</i> value	HR (95% CI)	<i>P</i> value	HR (95% CI)
Baseline IPSS (continuous)	0.30	—	—	—
Age (continuous)	0.88	—	—	—
Prostate volume on pretreatment MRI (cm ³)	<0.0001	1.01 (1.01-1.02)	0.43	—
Prostate V100 (continuous)	0.13	—	—	—
Prostate D90 (continuous)	0.02	1.013 (1.002-1.023)	0.09	—
Prostate V150 (continuous)	0.05	—	—	—
Urethra D20 (continuous)	0.41	—	—	—
Urethra D5 (continuous)	0.41	—	—	—
Urethra D1 (continuous)	0.93	—	—	—
Bladder V100	<.0001	1.12 (1.05-1.19)	0.29	—
Bladder D2cc (continuous)	<.0001	1.01 (1.00-1.01)	0.54	—
Bladder D1 (continuous)	<.0001	1.01 (1.00-1.01)	0.34	—
Bladder neck V100 (continuous)	0.1	—	—	—
Bladder neck D2cc	<.0001	1.04 (1.03-1.04)	<.0001	1.03 (1.03-1.04)
HI ((Prostate V100-V150)/V100)	.07	0.56 (0.30-1.06)	0.2	—
Use of neoadjuvant ADT (yes vs. no)	.42	—	—	—
Choice of isotope (Pd103 vs. I125)	.94	—	—	—
Definitive treatment vs. combined therapy with EBRT	<.0001	1.49 (1.25-1.78)	0.008	1.32 (1.08-1.63)
Number of seeds (continuous)	<0.0001	1.01 (1.01-1.02)	0.24	—
Number of needles implanted (continuous)	<0.0001	1.07 (1.04-1.10)	0.12	—
Diabetes (yes vs. no)	0.35	—	—	—
Smoking habits (current vs. former vs. never vs. unknown)	0.64	—	—	—
Use of PDE-5I at diagnosis (yes vs. no)	0.66	—	—	—

Abbreviations: ADT = androgen-deprivation therapy; CI = confidence interval; HI = homogeneity index; HR = hazard ratio; EBRT = intensity-modulated radiotherapy; IPSS = International Prostate Symptom Score; MRI = magnetic resonance imaging; PDE-5I = phosphodiesterase type 5 inhibitor.

Table 3

Receiver operator curve analysis for acute and late urinary toxicity

Variables	Area under the curve	P value	(95% CI)
<i>Acute urinary toxicity</i>			
Prostate V100>90%	.51	.63	.
Prostate D90>100%	.51	.58	.
Prostate V150 >60%	.50	.94	.
Urethra D20>130%	.50	.81	—
Bladder neck D2 cc>50%	.697	<.0001	.66-.73
<i>Late urinary toxicity</i>			
Prostate V100>90%	.53	.22	—
Prostate D90>100%	.53	.19	—
Prostate V150 >60%	.54	.06	—
Urethra D20>130%	.52	.40	—
Bladder neck D2 cc>50%	.620	<.0001	.57-.67

Abbreviations: CI = confidence intervals.

Table 4

Univariate and multivariate analysis for late urinary toxicity

	Univariate		Multivariate	
	<i>P</i> value	HR (95% CI)	HR (95% CI)	<i>P</i> value
Baseline IPSS (continuous)	.08	1.03 (.99-1.06)	.38	—
Age (continuous)	.33	—	—	—
Prostate volume on pretreatment MRI	.004	1.01 (1.00-1.02)	.13	—
Prostate V100 (continuous)	.01	1.03 (1.00-1.06)	.8	—
Prostate D90 (continuous)	<.0001	1.02 (1.01-1.03)	.55	—
Prostate V150	.001	1.02 (1.01-1.03)	.35	—
Urethra D20 (continuous)	.17	—	—	—
Urethra D5 (continuous)	.39	—	—	—
Urethra D1 (continuous)	.99	—	—	—
Bladder V100	<.0001	1.2 (1.1-1.3)	.22	—
Bladder D2cc	<.0001	1.01 (1.00-1.02)	.29	—
Bladder neck V100	.84	—	—	—
Bladder neck D2cc	<.0001	1.02 (1.01-1.03)	.006	1.02 (1.00-1.03)
Bladder neck D1cc	<.0001	1.01 (1.01-1.02)	.09	—
HI	.002	.17 (.06-.52)	.04	.16 (.03-.9)
Use of neoadjuvant ADT (yes vs. no)	.41	—	—	—
Choice of isotope (Pd103 vs. I125)	.64	—	—	—
Definitive treatment vs. combined therapy with EBRT	.18	—	—	—
Number of seeds (continuous)	.07	1.01 (.99-1.02)	.42	—
Number of needles implanted (continuous)	<.0001	1.01 (1.05-1.16)	.011	1.09 (1.02-1.16)
Diabetes (yes vs. no)	.84	—	—	—
Smoking habits (current vs. former vs. never vs. unknown)	.42	—	—	—
Use of PDE-5I at diagnosis (yes vs. no)	.14	—	—	—

Abbreviations: ADT = androgen-deprivation therapy; CI = confidence interval; HI = homogeneity index; HR = hazard ratio; EBRT = intensity-modulated radiotherapy; IPSS = International Prostate Symptom Score; MRI = magnetic resonance imaging; PDE-5I = phosphodiesterase type 5 inhibitor.