Clinical Investigation

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

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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 with the standard dosimetric variables. These data support the inclusion of bladder neck constraints into brachytherapy treatment planning, inasmuch as constraining the dose to this region may decrease urinary-related symptoms after treatment.

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).

Methods and Materials: From July 2002 to January 2013, 927 patients with prostate cancer (median age, 66 years) underwent LDR brachytherapy with Iodine 125 (n = 753) or Palladium 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 the computed tomographic (CT) scan on day 0 after implantation 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 with the Common Terminology Criteria for Adverse Events, version 4. Clinical and dosimetric factors associated with AUT and LUT were analyzed with Cox regression and receiver operating characteristic analysis to calculate area under the receiver operator curve (ROC) (AUROC).

Results: Grade 2 AUT and grade 2 LUT occurred in 520 patients (56%) and 154 patients (20%), respectively. No grade 4 toxicities were observed. Bladder neck D2cc retained a significant association with AUT (hazard ratio [HR], 1.03; 95% confidence interval [CI], 1.03-1.04; P < .0001) and LUT (HR, 1.01; 95% CI, 1.00-1.02; P = .014) on multivariable analysis. In a comparison of bladder neck with the standard dosimetric variables by use of ROC analysis (prostate V100 > 90%, D90 > 100%, V150 > 60%),
urethra D20 130%), bladder neck D250% was shown to have the strongest prognostic power for AUT (AUC, 0.697; P < 0.001) and LUT (AUC, 0.620; P < 0.001).

Conclusion: Bladder neck D250% was the strongest predictor for grade 3 and 4 urinary toxicity in patients treated with LDR brachytherapy. These data support inclusion of bladder neck constraints into brachytherapy planning to decrease urinary toxicity.

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Introduction

Low-dose-rate (LDR) brachytherapy with permanent seed implantation with or without supplemental external beam radiation therapy (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 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 in the use of permanent seed implantation, including maintaining a urethra V50% and urethra V30% 25% (10).

However, the most critical anatomical structure associated with prostate radiation therapy 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 neo-adjuvant 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 and have found an association between the dose to the urethra/basal prostate and urinary toxicity (3, 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.

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.

Methods and Materials

Patient and treatment characteristics

Before this retrospective study was conducted, institutional review board approval was obtained. From July 2002 to January 2013, 927 consecutive patients with a median age of 66 years (interquartile range [IQR], 60-71 years) were treated at our institution, with a median follow-up time of 42.5 months (IQR, 28-61 months) and a minimum follow-up time of 12 months. Patients prior to this time period were not included in the current analysis. Patients with low-risk or favorable intermediate-risk prostate cancer as defined by the National Comprehensive Cancer Network (NCCN) risk classification, with only 7.4% of patients having high-risk disease (69). All patients had confirmation of the diagnosis with biopsy review by a urologic pathologist at our institution before treatment.

Magnetic resonance imaging (MRI) was obtained before treatment for patients; MRI was not required for treatment, and the reasons for not obtaining MRI included patient refusal and inability to undergo MRI because of pacemaker/defibrillator or other implant placement.

Short-course ADT was administered to 249 patients (22%) for a maximum of 6 months and was routinely discontinued after the end of the LDR procedure or EBRT. In general, patients with large gland size (cm3) were treated with 3 months neoadjuvant ADT for cytoduction before brachytherapy. Definitive brachytherapy was delivered to 478 patients (51.6%) with the use of Iodine 125 (125I) seeds to a total dose of 144 Gy. Brachytherapy was delivered as a boost followed by EBRT was delivered to 449 patients (48.4%) with the use of Palladium 103 (103Pd) (100 Gy) and 125I (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 IPSS score was 5 (range, 3-9). Patient characteristics are provided in the supplementary material.

Study design

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

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Foley-defined urethra immediately inferior to the easily visualized Foley balloon), these contours are very consistent, with volume standard deviation of only 0.21 cm³ (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 E1 available at www.redjournal.org. In addition, the homogeneity index (HI), defined as HI = [Prostate V100 / Prostate V150] / 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. Briefly, the patients were intubated under general anesthesia, with intravenous dexamethasone (8 mg) given at the 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 averted gel was applied to maximize urethral visualization, and axial ultrasound images of the prostate were subsequently acquired at 6 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 3-dimensional reconstruction. Needle positions were identified and reconstructed by the use of template coordinates. An inverse planning system using 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 with a Mick applicator (Mick Radio-Nuclear Instruments, Inc, Mount Vernon, NY) under ultrasonographic and fluoroscopic image guidance according to the approved treatment plan. A day 0 postimplantation 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 2007 to 2010. Since 2010, a portable CT fluoroscopic unit was used to maintain real-time kilovoltage cone beam CT images with the patient in the supine position immediately after the procedure and before anesthesia reversal.

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

Outcome measurement

The patients’ IPSS scores were obtained before the brachytherapy procedure and repeated at each follow-up visit. Patients were evaluated every 3 months for the first year.
through a perineal template under sagittal and axial transrectal and fluoroscopic image guidance according to the approval prescription dose) was generated. Radioactive seeds were patterned with respect to the predetermined dose-volume constraints and inserted into the peripheral substance of the prostate gland to obtain real-time kilovoltage cone beam CT images with the patient in the supine position immediately after the procedure to facilitate fiducialization. Needle positions were identified and reconstructed on each axial image for computer-based three-dimensional dose reconstruction. Contours of the target volume and organs at risk were drawn on the treatment planning CT scan. Needle positions were transferred into the brachytherapy treatment planning system for treatment planning. A conformal treatment plan and associated seed-loading model were created for each patient. Ultrasound image guidance. Transurethral aerated gel was used. A conformal treatment plan and associated seed-loading model were created for each patient. The LDR seed implantation procedure and intraoperative ultrasound-guided transperineal technique was used.

A conformal treatment plan and associated seed-loading model were created for each patient. The LDR seed implantation procedure and intraoperative ultrasound-guided transperineal technique was used.

Contour of bladder neck on computed tomographic scan on day 0 after implantation.

**Fig. 1.** Contour of bladder neck on computed tomographic scan on day 0 after implantation.

Acute grade 2 and grade 3 urinary toxicity occurred in 51 patients (55.9%) and 1 patient (0.1%), respectively. No acute grade 4 toxicity was observed in this cohort.

Acute grade 2 and grade 3 urinary toxicity occurred in 51 patients (55.9%) and 1 patient (0.1%), respectively. No acute grade 4 toxicity was observed in this cohort.

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 with 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.<0.05 was considered statistically significant.

Multivariable models were developed incorporating factors with threshold values of 1 on univariate analysis.

For factors with a high likelihood of interaction (ie, prostate volume on pretreatment MRI (P<0.001), prostate D90 (0.2), bladder V100 (P<0.001), bladder D2cc (P<0.001), bladder D1cc (P<0.001), bladder neck D2cc (P<0.001), the number of implanted needles (P<0.001) and seed Dcc (P<0.001), and brachytherapy as definitive treatment versus combined treatment), these factors were associated with grade 2 AUT as shown in Table 1. 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<0.001) and brachytherapy as definitive treatment versus combined treatment (HR, 1.3; 95% CI, 1.08-1.6; P<0.01) retained significant association with AUT, as shown in Table 2. When the bladder neck D2cc was compared with the other published dosimetric constraints by use of ROC analysis (prostate V100 90%, D90 >100%, V150 >60%, urethra D20 130%), the bladder neck D2cc >50% (AUC 0.697, P<0.001) was shown to have the strongest prognostic power for AUT as shown in Table 3.

Late grade 2 and grade 3 urinary toxicity occurred in 154 patients (17%) and 31 patients (3%), respectively. No late grade 4 toxicity was observed. On univariate analysis, prostate volume on pretreatment MRI (P<0.001), prostate V100 (P<0.001), prostate V150 (P<0.001), bladder V100 (P<0.001), bladder V150 (P<0.001), bladder V100 (P<0.001), bladder D2cc...
Acute grade 2 and grade 3 urinary toxicity occurred in 519 patients. On univariate analysis, prostate volume on pretreatment MRI (cm³), age, smoking habits, isotope, diabetes, use of neoadjuvant ADT, definitive treatment vs combined therapy with EBRT, number of seeds (continuous), and number of implanted needles (continuous) were associated with LUT.

On multivariate analysis, bladder neck D2cc (HR, 1.02; 95% CI, 1.00-1.03; \( P < 0.001 \)), HI (HR, 0.16; 95% CI, 0.03-0.9; \( P < 0.001 \)), and the number of implanted needles (continuous) retained significant association with LUT. The bladder neck D2cc > 50% (AUC, 0.62; \( P < 0.001 \)) was the strongest predictor for LUT according to ROC analysis.

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 months). Patients with bladder neck D2cc > 50% had a significantly faster median time to urinary symptom resolution on log rank test, as shown in Figure 2.

Discussion

Our findings provide strong evidence that the bladder neck/trunk 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 in which we demonstrated that, among patients treated with IGRT alone, the dose to the bladder neck/trigone is strongly associated with urinary toxicity.
The bladder trigone appears to be responsible for micturition by contracting during bladder filling, helping to keep the urinary retention. Our present study represents an extension of a previous report in which we demonstrated that, among patients treated with IGRT alone, the dose to the bladder (15). We conducted this present study to assess the impact of the dose to the bladder neck on urinary toxicity in patients treated with 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 grade 2 urinary toxicity, respectively. Bladder neck D2cc (HR, 1.02; 95% CI, 1.00-1.03; 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, 1.09; 95% CI, 1.02-1.16; P = .014) was significantly correlated with LUT on multivariable analysis, and bladder neck D2cc > 50% (AUC, 0.620 P < .0001) was the strongest predictor for LUT according to ROC analysis, with other published factors again serving no better than random chance.

Table 4: Univariate and multivariate analysis for late urinary toxicity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td>HR (95% CI)</td>
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<tr>
<td>Baseline IPSS (continuous)</td>
<td>.08</td>
<td>1.03 (0.99-1.06)</td>
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<tr>
<td>Age (continuous)</td>
<td>.33</td>
<td>-</td>
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<td>Prostate volume on pretreatment MRI</td>
<td>.04</td>
<td>1.01 (1.00-1.02)</td>
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<tr>
<td>Prostate V100 (continuous)</td>
<td>.01</td>
<td>1.03 (1.00-1.06)</td>
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<tr>
<td>Prostate D90 (continuous)</td>
<td>&lt; .0001</td>
<td>1.02 (1.01-1.03)</td>
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<tr>
<td>Prostate V150</td>
<td>.005</td>
<td>1.02 (1.01-1.03)</td>
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<tr>
<td>Urethra D20 (continuous)</td>
<td>.17</td>
<td>-</td>
</tr>
<tr>
<td>Urethra D5 (continuous)</td>
<td>.39</td>
<td>-</td>
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<tr>
<td>Urethra D1 (continuous)</td>
<td>.99</td>
<td>-</td>
</tr>
<tr>
<td>Bladder V100</td>
<td>&lt; .0001</td>
<td>1.2 (1.1-1.3)</td>
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<tr>
<td>Bladder D2cc</td>
<td>&lt; .0001</td>
<td>1.01 (1.00-1.02)</td>
</tr>
<tr>
<td>Bladder neck V100</td>
<td>.84</td>
<td>-</td>
</tr>
<tr>
<td>Bladder neck D2cc</td>
<td>&lt; .0001</td>
<td>1.02 (1.01-1.03)</td>
</tr>
<tr>
<td>Bladder neck D1cc</td>
<td>&lt; .0001</td>
<td>1.01 (1.01-1.02)</td>
</tr>
<tr>
<td>HI</td>
<td>.002</td>
<td>0.17 (0.06-0.52)</td>
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<tr>
<td>Use of neoadjuvant ADT (yes vs no)</td>
<td>.41</td>
<td>-</td>
</tr>
<tr>
<td>Choice of isotope (103Pd vs 125I)</td>
<td>.64</td>
<td>-</td>
</tr>
<tr>
<td>Definitive treatment vs combined therapy with EBRT</td>
<td>.18</td>
<td>-</td>
</tr>
<tr>
<td>Number of seeds (continuous)</td>
<td>.07</td>
<td>1.01 (0.99-1.02)</td>
</tr>
<tr>
<td>Number of needles implanted (continuous)</td>
<td>&lt; .0001</td>
<td>1.01 (1.05-1.16)</td>
</tr>
<tr>
<td>Diabete (yes vs no)</td>
<td>.84</td>
<td>-</td>
</tr>
<tr>
<td>Smoking habits (current vs former vs never vs unknown)</td>
<td>.42</td>
<td>-</td>
</tr>
<tr>
<td>Use of PDE-5 at diagnosis (yes vs no)</td>
<td>.14</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: 103Pd: Palladium 103; 125I: Iodine 125; ADT: androgen-deprivation therapy; CI: confidence interval; HI: homogeneity index; HR: hazard ratio; EBRT: external beam radiation therapy; IPSS: International Prostate Symptom Score; MRI: magnetic resonance imaging; PDE-5: phosphodiesterase type 5 inhibitor.

Bladder neck D2cc dose of 1%: 3% and 2% increase in the risk of acute and late grade 2 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, 1.09; 95% CI, 1.02-1.16; P = .014) was significantly correlated with LUT on multivariable analysis, and bladder neck D2cc > 50% (AUC, 0.620 P < .0001) was the strongest predictor for LUT according to ROC analysis, with other published factors again serving no better than random chance.

After permanent LDR brachytherapy to the prostate, AUT is frequent; the intensity of symptoms usually peaks 1 to 3 months after the brachytherapy procedure and returns to baseline after approximately 12 months. Keyes et al (11) have reported a shorter time to resolution of elevated IPSS in patients with higher baseline IPSS. Kaplan-Meier survival curves: time to International Prostate Symptom Scores resolution according to the bladder neck D2cc dose.
Although the ABS has established conservative urethral placement as the primary constraint for the urethra, there does not seem to be a clear threshold dose for the urethra that reliably predicts urethral toxicity. No dose constraints have been firm established for the bladder, in whole or in part.

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 brachytherapy and external beam radiotherapy. In our present study, a higher HI was correlated with a higher rate of LUT (HR, 0.16; 95% CI, 0.03-0.9; P = 0.04) in patients treated with LDR, neck D2cc to 50% did not affect the implant quality; although it was not associated with AUT. Prostate V150/ V100 dosimetric criteria were respected.

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 implantation, suggesting the importance of outlining the urethral base. Steggerda et al. proposed bladder neck D0.5 cc > 175 Gy (120.7%) of the prescription dose as a potential dose constraint for patients treated with definitive brachytherapy. The authors did not specify the mean bladder neck volume contoured. The D0.5 cc corresponds most probably to the maximum dose received by the bladder neck, which in our study would be close to the D2cc because the minimum bladder neck volume contoured was 2 cm.

The major strengths of our study are the large number of patients, the consistent delineation of the bladder neck structure on the day 0 postimplantation 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 because 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 often used to evaluate the homogeneity of the implant and correlates with urethral strictures. The ratio of prostate target volume, and increasing the HI could potentially decrease LUT. As yet, no HI threshold has been established in the literature.

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

Conclusions

Bladder neck D2 < 50% was identified as a strong predictor of 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, because 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 under way at our institution to address the validity of the proposed bladder neck dose constraint.

References


In this study has the advantage of being easily applicable the day0 intraoperative CT scan, which avoids unnecessary assessment of the validity of the proposed bladder neck dose decrease urinary-related symptoms after treatment. Our planning, because constraining the dose to this region may depend on intraoperative computer-optimized perineal ultrasound-guided prostate brachytherapy. The feasibility of bladder neck constraints into brachytherapy treatment planning for prostate cancer: A perspective of the recent literature. Although this study does support the definition of a new risk classification system for prostate cancer patients having intermediate and high-risk features.
