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Reductions in prostatic doses are associated with less acute morbidity in patients undergoing Pd-103 brachytherapy: Substantiation of the rationale for focal therapy

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Abstract

Purpose/Objectives—Interest in prostate dose reduction or focal treatment exists due to expected reductions in treatment morbidity. Prior analyses have not generally corroborated relationships between prostate or urethral dose and urinary toxicity after brachytherapy, but such analyses have been performed on cohorts all receiving the same prescribed dose. We analyzed patients treated to differing prescription doses to assess acute urinary morbidity with dose reduction.

Materials/Methods—Patients treated with Pd-103 to either 125Gy or 90–100Gy were compared using International Prostate Symptom Score (IPSS) at 1-month post-implant. Patients in 90–100Gy cohort began EBRT after their 1-month assessment, thus toxicities were measured prior to contribution from EBRT. Patient/treatment characteristics were compared to verify subgroup homogeneity. Dose and change in IPSS 1 month after treatment was assessed using a multivariate linear regression model.

Results—One hundred ninety-one and 41 patients were treated with 125Gy vs 90–100Gy, respectively. Pre- and post-implant prostate volumes and initial IPSS were similar between groups. Higher prescription dose and increased pre-treatment IPSS were independent predictors of increased 1-month IPSS. Additionally, every 10 percentage point additional prostate volume receiving a given dose was associated with increase in IPSS post treatment for the same level of pre-treatment IPSS.

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Conflict of Interest: none.

Conclusion—Lower prescription dose and decreased volume of high dose regions to the prostate correlated with reduced acute urinary morbidity after brachytherapy. Our findings suggest that focal treatment approaches with modest dose reductions to sub-regions of the prostate may reduce acute morbidity and potentially expand the number of patients eligible for brachytherapy.

Keywords

Prostate cancer permanent seed brachytherapy; patient reported outcomes; radiation toxicity; International Prostate Symptom Score; dosimetry; focal prostate treatment

Introduction

Permanent low dose rate (LDR) implant prostate brachytherapy is a treatment modality which targets the whole prostate with a 2–3 mm margin. Cancer-specific outcomes are comparable to prostatectomy and external beam radiation as a definitive monotherapy in low and intermediate risk patients [1]. In high-risk patients, brachytherapy combined with external beam and androgen deprivation therapy demonstrated improved progression free survival versus external beam and ADT alone [2]. Although brachytherapy is considered a standard treatment modality for prostate cancer, it is not consistently recommended given concerns for acute and late-effect urinary, rectal and sexual morbidity.

Acute urinary symptoms represent a major form of treatment-related morbidity after prostate brachytherapy, and indeed limit the pool of patients who are eligible for the procedure. Multiple studies have demonstrated that at least part of the urinary morbidity following brachytherapy is related to the dose received by the urethra [3, 4]. Additionally, Allen et al. reported that the maximum post-treatment IPSS was best predicted by pre-implant IPSS and the maximum apical urethral dose [5]. However, urethral dose has not uniformly demonstrated to be a predictor of increased acute urinary morbidity [6, 7]. One weakness of prior reports is that such analyses have been performed on patients that were treated to the same prescribed dose, therefore limiting the variability of doses received by prostate and urethra.

The primary intent of this study was to analyze patients treated to differing prescription doses to assess for effects of dose reduction on acute urinary morbidity, and to estimate the magnitude of such effects.

Materials and Methods

The study was performed with approval of the Institutional Internal Review Board. The purpose of this study was to analyze patients treated to differing prescription doses to assess for effects of dose reduction on acute urinary morbidity. Patients treated with Pd-103 to either 125Gy (full-dose) or 90–100Gy (reduced-dose) were assessed using patient-reported International Prostate Symptom Score (IPSS) at 1-month post-implant (based on published evidence showing urinary morbidity after Pd-103 peaks at 1-month). Patients in 90–100Gy cohort were planned to be given supplemental external beam radiation therapy (EBRT) to 45Gy after their 1-month assessment, thus toxicities were measured prior to any contribution from EBRT and at the time when acute urinary morbidity is at or near its maximum [8].

Baseline patient characteristics such as pre- and post-treatment prostate volumes, pre-implant IPSS, and number of seeds and needles used during the procedure were compared to assess comparability of the distributions between the treatment groups.

Dosimetric parameters that were assessed included prostate V100Gy, V125Gy, 150Gy, 175Gy, and V200Gy (percent of the prostate volume receiving 100 Gy, 125 Gy, 150 Gy, etc.), urethral V100Gy, and V150Gy (urethral volume in cc's receiving 100Gy and 150Gy), prostate D25, D50, D80, and D90 (Dose received by 25%, 50%, etc. of the prostate) and urethral D10, D20, D30, D50 (Dose received by 25%, 30%, etc. of the urethra). (Given the differing dose prescriptions, we analyzed by absolute dose rather than percentage of prescribed dose.) All treatment planning was performed on commercially available software (Variseed V8.0, Varian Medical Systems, Palo Alto, CA). The selected source type for all cases was TheraSeed 200 (Pd-103; Theragenics, Norcross GA). Source activities were 2.5U for the patients treated with a prescription dose of 125 Gy and 2.0–2.2 in the patients treated to 90–100 Gy. Patients underwent Day 1 post-implant CT for dosimetric analysis, with urinary catheter in place allowing for direct identification and contouring of the urethra. Urethra was defined in craniocaudal direction from just below catheter balloon to apex of prostate. The goal of this analysis was to assess toxicity related to the dosing of Pd-103 treatment and report IPSS change associated with dosimetric parameters.

Statistical Analysis

Data are summarized as means and standard deviations (SD) or percentage for continuous and binary variables, respectively. Treatment dose was used as a binary variable categorized as full dose (125Gy) or reduced dose (90/100Gy). The relationship between dose and change in IPSS after treatment was assessed using linear regression model with robust variance estimate with IPSS change as the dependent variable and dose as the primary predictor [9]. This univariate relationship was further adjusted to include potential confounders, such as pre-treatment IPSS, number of seeds and pre-treatment prostate volume using a multiple linear regression model. The same models were used to look at dosimetric parameters, such as prostate volume receiving certain dose, after adjustment for pre-treatment IPSS. From these models, marginal effects associated with various volumes by dose were calculated with standard errors estimated by the delta method [10].

All tests were two-sided and were conducted at 0.05 level of statistical significance. Stata 14 was used for data analysis (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Results

Treatment Characteristics

Treatment characteristics are displayed in Table 1. One hundred and ninety one patients were treated with full-dose brachytherapy (125 Gy) and 41 patients were treated with reduced-dose brachytherapy (21 to 90 Gy and 20 to 100 Gy). The average pre-implant and post-implant prostate volumes were similar between the full-dose and reduced-dose groups, 33.0 cc (SD = 9.1 cc) versus 32.3 cc (SD = 10.8 cc) and 42.5 (SD = 11.6 cc) versus 41.5 (SD

= 12.1 cc), respectively ($p = 0.65$ and $p = 0.64$). The mean pre-implant IPSS was 6.2 (SD = 4.4) for the full-dose group and 6.0 (SD = 4.6) for the reduced-dose group ($p = 0.87$). A reduction of the prescription translated into a reduction in both the average number of Pd-103 seeds (80.2 versus 72.9, $p = 0.006$) and needles (35.7 versus 30.6, $p < 0.001$) used during the procedure.

Figure 1 shows prostate and urethral dose-volume histograms comparing patients treated with full-dose Pd-103 prostate brachytherapy to reduced-dose treatment. Dose and volume values represent mean values for each treatment cohort. As expected, the dosimetric parameters were uniformly increased for the full-dose group compared to the reduced-dose cohort.

Urinary Morbidity

Figure 2 shows the pre-treatment and one month post treatment IPSS score by the dosing group. The pre-treatment IPSS were on average comparable with mean IPSS score in the reduced Pd-103 dose group 6.0 (4.6) versus 6.2 (4.4) in the full-dose group, p -value = 0.871). The post-treatment IPSS were higher in both dosing groups. However, patients treated with reduced-dose Pd-103 low-dose rate brachytherapy experienced a 4.5 point lower average increase in one month post-implant IPSS (95% CI: between 1.5 to 7.4-point lower) compared to the full-dose treatment group ($p = 0.003$).

Table 2 displays treatment and patient-related predictors of developing increased IPSS one month post-brachytherapy. The estimated difference in IPSS increase post treatment did not appreciably change after adjustment for pretreatment IPSS, number of seeds and pre-treatment prostate volume (p -value=0.001). Additionally, pre-implant IPSS was positively associated with change in IPSS at one month post implant ($p < 0.001$). The number of brachytherapy seeds implanted ($p = 0.594$) and pre-implant prostate volume ($p = 0.113$) were not associated with increasing one-month IPSS in the multivariable model (table 2).

Dosimetric parameters were found to be statistically significant predictors for increasing one month post-implant IPSS after adjustment for pre-treatment IPSS. Every 10 percentage point additional prostate volume receiving a given dose was associated with increase in IPSS post treatment for the same level of pre-treatment IPSS; the estimates by dose were as follows: 1.1 (95%CI: -0.4 to 2.7, p -value = 0.151) increase for 100Gy, 1.2 (95%CI: 0.0 to 2.5, p -value = 0.050) increase for 125Gy, 1.0 (95%CI: 0.03 to 1.9, p -value = 0.044) increase for 150Gy, 0.8 (95%CI: -0.002 to 1.6, p -value = 0.051) increase for 175Gy, and 0.7 (95%CI: -0.09 to 1.52, p -value = 0.080) increase for 200Gy. These linear slopes resulted in the estimated post-treatment IPSS changes presented in Figure 3. The results show that for the same prostate volume receiving different doses, the estimated change in IPSS is higher for higher doses and for the same dose, increase in the percent of prostate volume receiving that dose is associated with a greater change in IPSS.

Discussion

In general, analyses in the modern era have not consistently corroborated relationships between prostate or urethral dose and urinary toxicity. Although early experiences suggested

associations between urethral dose and toxicity, more contemporary analyses in which the urethral doses have been lower (100–140% of prescribed dose) have generally not found evidence to link urinary morbidity with urethral dosimetry. Neill and colleagues segmented the prostate into equal thirds (proximal, mid, and apical) and investigated whether the location and dose of urethral radiation increased post-brachytherapy IPSS. They demonstrated that greater baseline IPSS and preoperative TRUS volume were predictive of IPSS outcomes at 1 month, but were unable to correlate regional urethral dosimetry to influence the nature or extent of urinary symptoms after prostate brachytherapy [6]. Crook et al. analyzed predictors of developing acute urinary retention post permanent seed prostate brachytherapy. Twenty men who experienced retention were compared to 130 patients without the complication. Prostate volume and prior hormone use were independent predictors of developing acute urinary retention; however, prostate and urethral dosimetric parameters were not found to be significant [7]. These findings are corroborated by other groups as well [6, 11, 12].

A few other analyses have supported the role of reducing dose to critical urological anatomical structures in order to decrease post-brachytherapy urinary morbidity. Singhal et al. performed a dosimetric comparison for patients who developed urethral strictures compared to patients who did not. They identified pre-treatment IPSS, urethra D30Gy and D5Gy, and intraprostatic urethra with 5-mm margin V200 at the apex as having the highest ability to predict the development of urinary strictures [13]. Allen et al. utilized regional urethral dosimetry to predict urinary morbidity for patients treated with I-125. The maximum dose received by the prostate apex and genitourinary diaphragm predicted the greatest increase in IPSS, and the maximum IPSS was best predicted by preimplant IPSS and the maximum apical urethral dose [5]. Another study by Hathout et al. correlated acute and late urinary symptoms after brachytherapy with dose to bladder neck (dose to 2cc), but this has yet to be confirmed in other studies [14]. Pinkawa et al. analyzed health-related quality of life following prostate brachytherapy and recommended a prostate D90 < 170 Gy and a base of seminal vesicle D10 < 190 Gy (as an indicator of the dose to the bladder neck and urethral sphincter) to maintain a satisfactory urinary function. Higher rates of pad usage, worse urinary bother score and urinary function score during the acute period were associated with doses higher than the threshold of D10 [15].

However, all of these studies have been limited in that such analyses have been performed on patients receiving the same prescribed dose. In this study, we compared urinary morbidity in patients treated with Pd-103 LDR brachytherapy to differing prescription doses and demonstrated that one month post-implant IPSS is decreased with prescription dose- and absolute prostate dose reduction. In our analysis, prescription dose as well as volume reduction to high-dose regions of the prostate and urethra were correlated with reduced urinary morbidity one month post-implant on univariate analysis. Our findings are significant as consideration increases for prostate brachytherapy focal treatment approaches, based on the expectation that reduced doses to uninvolved or spared regions of prostate will reduce treatment morbidity.

Al-Qaisieh et. al. performed a dosimetric analysis of LDR prostate brachytherapy plans which compared whole-gland, hemi-gland, and ultra-focal treatment and demonstrated a

reduced number of needles and seeds used during implantation, and also reduced mean urethral doses to 205.9 Gy, 191.4 Gy, and 92.4 Gy, respectively [16]. Cosset and colleagues published a small series of patients treated with focal prostate brachytherapy which included patients with very limited localized tumors confirmed with at least two series of prostate biopsies and high-resolution MRI [17]. The mean volume treated was 34% of the total prostate and IPSS was significantly reduced at 6 months compared to patients treated with whole prostate brachytherapy. However, short interval follow-up restricted analysis of cancer-specific outcomes. Despite a paucity of evidence, the available preliminary data for focal brachytherapy suggest urinary morbidity may be decreased with equivalent oncologic outcomes and active trials accruing longer follow-up monitoring are anticipated in the near future.

This study demonstrates that focal treatment approaches with modest dose reductions to subregions of the prostate may reduce acute urinary morbidity, and additional studies in focal prostate brachytherapy are warranted.

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Abbreviations

LDR	low dose rate
IPSS	International Prostate Symptom Score
EBRT	external beam radiation therapy
SD	standard deviation

Figure 1.

Dose/Volume histograms. (A) Prostate volume versus dose shows increased dose to prostate for full-dose group compared to reduced-dose group. (B) Urethra volume versus dose demonstrates uniformly increased dose to urethra for full-dose group compared to reduced-dose group.

Figure 2.
Average IPSS pre- and post-treatment by dose

Panel A: Δ IPSS vs V100 Gy Panel B: Δ IPSS vs V125 Gy Panel C: Δ IPSS vs V150 Gy Panel D: Δ IPSS vs V175 Gy Panel E: Δ IPSS vs V200 Gy **Figure 3.**

Estimated change in IPSS across different percentages of prostate volume receiving selected doses: (Panel A: 100 Gy, Panel B: 125 Gy, Panel C: 150 Gy, Panel D: 175 Gy, and Panel E: 200 Gy). The estimated change is adjusted for the original IPSS level. The shaded area represents the confidence intervals around the estimated change in IPSS for each percentage of prostate volume receiving a given dose.

Table 1

Treatment Characteristics. Values listed as means and standard deviations (SD) for continuous variables and percent for catheter use

Variable	Full-dose 125 Gy (n=191)	Reduced-dose 90–100 Gy (n=41)	P-value
	Mean (SD)		
Pre-implant prostate volume	33.0 (9.1)	32.3 (10.8)	0.650 *
Post-implant prostate volume	42.5 (11.6)	41.5 (12.1)	0.635 *
Consult IPSS	6.2 (4.4)	6.0 (4.6)	0.868 *
Number of seeds	80.2 (15.1)	72.9 (14.9)	0.006 *
Number of needles	35.7 (7.5)	30.6 (7.4)	<0.001 *
Catheter use (%)	7.3	0	0.137 **

*
from two-sided t-test

**
from Fisher's exact test

Table 2

Results of linear regression model for post-treatment change in IPSS score

	Univariate Analysis		Multivariate Analysis	
	Estimated Beta Coefficient [95% Confidence Intervals]	p-value	Estimated Beta Coefficient [95% Confidence Intervals]	p-value
Dose: 90/100 Gy vs. 125 Gy	-4.445 **	0.003	-4.609 **	0.001
	[-7.369,-1.521]		[-7.393,-1.825]	
Pre Treatment IPSS (per 1 point increment)	-0.567 ***	<0.001	-0.578 ***	<0.001
	[-0.784,-0.349]		[-0.793,-0.362]	
Number of Seeds (per 1 additional seed)	0.0576	0.082	-0.0265	0.594
	[-0.00738,0.123]		[-0.125,0.0715]	
Pre-treatment volume (per 1 cc increment)	0.103	0.081	0.140	0.113
	[-0.0129,0.220]		[-0.0337,0.314]	
<i>N</i>	231		231	

95% confidence intervals in brackets

*
 $p < 0.05$,**
 $p < 0.01$,***
 $p < 0.001$