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Clinical factors and dosimetry associated with the development of prostate brachytherapy–related urethral strictures: A matched case–control study

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ABSTRACT

PURPOSE: Urethral strictures are a rare complication of prostate brachytherapy (BXT), with prior studies showing radiation dose to the bulbomembranous urethra as being associated with stricture formation. This retrospective case–control study explored clinical and dosimetric parameters associated with the development of BXT-related urethral strictures.

METHODS AND MATERIALS: A cohort of 34 patients developed urethral strictures after BXT at our institution for the period of 2008–2014. Each case was matched with two controls (68 controls) that had not developed a urethral stricture according to similar baseline clinical and dosimetric parameters. Stricture development was compared with clinical (i.e., age, smoking status, diabetes, hypertension, vascular disease, International Prostate Symptom Score, hormones) and dosimetric (i.e., prostate, urethra, urethral segments [base, midgland, apex, extraprostatic, and 5 mm margin]) variables. Statistical modeling approaches such as univariate, multivariate, and subset selection methods for risk prediction were applied to identify parameter(s) with best predictive ability of toxicity. The performances of models were ranked according to Akaike information criterion score.

RESULTS: The results show that the R^2 statistic increases from 6%, when only one parameter is included in the model, to almost 33%, when all the parameters are included. The best-fit subset of parameters included pretreatment International Prostate Symptom Score sum, urethra D_{30} Gy, urethra D_5 Gy, and intraprostatic urethra with 5-mm margin V_{200} at the apex having the highest ability to predict the development of urinary strictures.

CONCLUSIONS: This study used statistical modeling, a novel approach in prostate BXT dosimetric studies, to identify a subset of parameters with predictive ability in identifying patients who develop urethral strictures.

Keywords: Urethral stricture; Low dose rate; Prostate; Brachytherapy; Stranded sources; Dosimetry

Introduction

Permanent interstitial low-dose-rate (LDR) prostate brachytherapy (BXT) is an effective treatment option for men with localized prostate cancer and has become a standard treatment with excellent long-term biochemical relapse–free and overall survival (1–3). LDR prostate BXT has gained popularity because of its safe toxicity profile with high doses that can safely be achieved to the prostate gland and low dose to the organs at risk.

Patients treated with LDR BXT often report significant urinary irritation or obstruction from baseline as compared

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with other treatment modalities such as surgery and external beam radiotherapy (EBRT). These symptoms can resolve near to baseline levels at 9 months (4) or up to 12 months after treatment (5). The higher grades of urinary toxicity (i.e., Grade 2−3 as defined in Common Terminology Criteria for Adverse Events, version 4.0) are caused by urethral stricture or stenosis.

Urethral stricture can be defined as narrowed segments of the urethra surrounded by spongiofibrosis, whereas urethral stenosis is defined as a constriction that occurs within the posterior urethra (6). Urethral stricture can occur as a consequence of radiation therapy in a small percentage of men and can manifest months or years after treatment. In theory, stricture/stenosis can happen at any location along the urethra course, but most (90%) occurs in the bulbomembranous (BM) portion (7).

In the earlier days of LDR prostate BXT, the incidence of stricture was reported as high as 12% (8), which has dropped to as low as 3.6% in more recent series (9), perhaps because of improvements in the dosimetric distribution of radioactive sources. Several studies have implicated clinical and treatment factors, such as preimplant urinary symptom score (10, 11), supplemental EBRT (12), adjuvant hormonal manipulation (13), age, prostate-specific antigen level, Gleason score (14), and cigarette smoking with urinary morbidity. Dosimetric studies have suggested that the region around the prostatic apex receiving high doses of radiation can contribute to urethral stricture formation. However, studies correlating dosimetry with urethral stricture formation have not identified a single parameter as being consistently predictive, suggesting that additional work is still necessary (9, 13, 14).

Recognizing that the likely dosimetric predictors of urethra stricture formation arise from the apex, this study analyzed these parameters in greater detail, while also studying additional (some of which have not been previously studied) parameters. This study presents a detailed evaluation of the incidence of urethral strictures in a cohort of LDR prostate BXT implants, while also identifying clinical and dosimetric predictors of urethral strictures using a sophisticated statistical model.

Methods and materials

Data

This study was approved by the local institutional ethics committee. Detailed clinical dosimetric data were collected for 916 consecutive patients treated with prostate BXT at our institution from 2008 to 2014, of which 34 patients developed urethral strictures. Each case with a urethral stricture was matched with two controls (68 controls) that had not developed a urethral stricture according to similar baseline International Prostate Symptom Score (IPSS), planned prostate volume, postimplant prostate V_{150}, and postimplant prostate D_{90} dosimetry parameters. Stricture development was compared with clinical (i.e., age, smoking status, diabetes, hypertension, vascular disease, IPSS, hormones) (Table 1) and dosimetric (i.e., prostate, urethra, urethral segments [i.e., base,

Table 1
Statistical analysis results using Wilcoxon test between clinical and dosimetric parameters and stricture toxicity (case−control comparison)

Parameters	Control	Standard error	Stricture	Standard error	*p* (Wilcoxon test)
a: Clinical parameters					
Age (y)	64.05	0.832	65.58	1.17	0.2089
Diabetes	0.1	0.037	0.24	0.074	0.0776
Vascular disease	0.13	0.041	0.21	0.07	0.341
Smoking	0.62	0.059	0.56	0.086	0.5726
Pretreatment IPSS	5.25	0.508	6.82	0.842	0.1314
Hormones	0.12	0.039	0.18	0.066	0.4215
Planned prostate volume (cc)	41.76	1.173	41.58	1.987	0.7333
Postimplant CT volume (cc)	48.68	3.146	42.29	4.52	0.2316
Gleason score total	6.38	0.059	6.38	0.085	1
Number of cores sampled	11.26	0.236	11.06	0.459	0.8067
Number of cores positive	3.76	0.285	4.18	0.477	0.5658
Pretreatment PSA (ng/mL)	6.81	0.395	6.33	0.488	0.6167
b: Dosimetric parameters					
Whole prostate					
Volume (cc)	50.81	1.067	51.15	1.451	0.6702
D_{90} (Gy)	157.5	1.483	157.03	2.452	0.8703
V_{200} (cc)	0	0.001	0.01	0.003	0.1227
V_{150} (cc)	0.11	0.02	0.15	0.026	0.1114
V_{100} (cc)	0.92	0.051	0.89	0.071	0.7764

IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen; D_{90} = the minimum dose in the hottest 90% of the target volume; V_{200} = percentage of organ volume receiving at least 200% of the prescribed dose; V_{150} = percentage of organ volume receiving at least 150% of the prescribed dose; V_{100} = percentage of organ volume receiving at least 100% of the prescribed dose.

Mean values shown, unless otherwise specified.