Urethral strictures following high-dose-rate brachytherapy for prostate cancer: Analysis of risk factors

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ABSTRACT

PURPOSE: High-dose-rate brachytherapy is an established technique to deliver a conformal dose of radiation to patients with prostate cancer. The William Buckland Radiotherapy Center has been performing high-dose-rate brachytherapy with external beam radiation treatment for prostate cancer since 1998 and has an extensive prospective database on all patients treated. The purpose of this analysis was to assess the risk of stricture formation and identify the predictive or causative factors.

METHODS AND MATERIALS: Three hundred fifty-four patients were treated between 1998 and 2008. Patients received one of three differing dose schedules: 20 Gy in four treatments (20 Gy/4), 18 Gy/3, and 19 Gy/2 during three sequential time periods. Nelson−Aalen cumulative hazard modeling was used to estimate risk of events over time. Potential risk factors, including dose, were identified and used in the analysis.

RESULTS: There were 45 patients who developed at least one stricture, an overall risk of 8.2% at 2 years. The 2-year risk of stricture formation was 3.4%, 2.3%, and 31.6% for 18 Gy/3, 20 Gy/4, and 19 Gy/2, respectively. Most strictures occurred in the bulbomembranous urethra (50%) or external sphincter region (33%). On multivariable analysis, the dose schedule used was the only significant predictor for increased stricture formation.

CONCLUSIONS: In our patients, those who received 19 Gy/2 were at a significantly higher risk of stricture formation. Most of these strictures were mild, requiring only one intervention but a 2-year stricture risk of 31.6% was striking, and we have modified our protocol. © 2013 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords: Prostate cancer; High-dose-rate brachytherapy; Urethral stricture; Late toxicity

Introduction

Local disease control in intermediate- and high-risk localized prostate cancer has been shown to have a dose response (1−3) but at a cost of increased normal tissue toxicity (4, 5). High-dose-rate brachytherapy (HDRB) in combination with external beam radiotherapy (EBRT) is an established dose escalation technique and offers outcomes at least comparable with EBRT-only studies (6−8). HDRB in combination

with EBRT has many advantages: it is more conformal than EBRT alone, the high dose per fraction exploits a postulated low α/β ratio of prostate cancer, and it reduces the overall treatment time. The optimal dose schedule for HDRB in combination with EBRT is yet to be established, but the dose per fraction has been increased to attempt to improve disease cure, reduce in-hospital time, and minimize discomfort for the patient. On the other hand, side effects may also occur as a result of such changes to the dose schedule. For example, the high dose per fraction may also increase the risk of late urethral toxicity. HDRB allows avoidance of structures outside the prostate gland, but the dose is difficult to limit and conform around the urethra, without reducing the prostate dose. The purpose of this analysis was to identify the stricture rate for patients over time; describe the strictures observed; and to identify any factor, including dose delivered, that may be contributing to stricture risk.

Patients and methods

We report on consecutive patients treated as part of a curative regimen that included EBRT and HDRB, from the commencement of our program in November 1998 until November 2008. All but 31 patients (8.8%) received concurrent hormone manipulation. Most patients were at intermediate or high risk (T category higher than T2a or prostate-specific antigen level higher than 10 ng/mL or Gleason score more than 6). Table 1 describes the patient characteristics.

External beam radiotherapy

Fourteen patients received the EBRT component at another center, for geographic reasons. The dose and fractionation for these patients is documented but the technique specifics were not. Ninety-six patients received the HDRB before the EBRT and 258 received HDRB after EBRT, depending on departmental logistics and theater list availability.

The clinical target volume was the prostate only, with departmental protocol margins added to create a planning target volume. For the patients treated at the William Buckland Radiotherapy Center, a three-dimensional conformal

technique was used. No attempt was made to treat the pelvic lymph nodes. The most common dose prescription was 46 Gy in 23 fractions (46 Gy/23), delivering 10 fractions daily for a fortnight, prescribed at the International Commission on Radiation Units and Measurements prescription point, using 18 MV photons. Patients were given instructions to have an empty rectum and "comfortably" full bladder for the treatment. Gold fiducial markers were used with a daily image-guided setup protocol since 2007.

High-dose-rate brachytherapy

In all patients, the HDRB was used as a "boost" in combination with EBRT. Since initiation of the HDRB program, three progressive, escalated fractionation schedules were used. From November 1998 to August 2000 a schedule of 20 Gy/4 was used. From September 2000 to June 2006, the schedule changed to 18 Gy/3. From July 2006 until November 2008, 19 Gy/2 was the standard. Two patients planned to receive 18 Gy/3, but received one fraction of 6 Gy and a second fraction of 10 Gy (16 Gy/2). This was because of the delays on Day 2, preventing a third fraction being delivered in a timely fashion.

The technique has been previously described (8). Up until July 2006, metal needles were used. Subsequently, plastic catheters were used in an attempt to reduce trauma. These needles or catheters were placed transperineally using transrectal ultrasound and fluoroscopic imaging for guidance. The needles or catheters were placed within the bladder lumen to ensure adequate coverage of the prostate base. Before September 2005, replanning was not routine. Since then, patients were re-CT imaged on the simulator CT but only replanned if the needle movement was estimated to be greater than 1 cm in the caudal direction. Since August 2008, all patients were replanned for each fraction.

The identification of the apex in the planning images is essential to ensure adequate coverage of the prostate. Before September 2005, this was identified based on the planning CT images. Since September 2005, a fiducial marker has been placed at the apex under ultrasound guidance and used as a reference to improve the identification of the apex on the planning CT images.

The target volume for the HDR component was the prostate with up to 6 mm in the cranial–caudal direction to account for microscopic extension and potential needle movement. Patients were planned using Plato (Nucletron, Veenendaal, The Netherlands) planning software until October 2009, since when the Nucletron Oncentra (Nucletron) planning system was routinely used.

All fractions were given over one admission, at least 6 h apart. The HDRB was delivered by ^{192}Ir source automatically afterloaded with a microSelectron [192]Ir (Nucletron). As the prescribed dose changed over time, the dose to the urethra was limited so that no more than 10% of the urethral volume was to receive greater than 120% of the prescribed dose ($D_{10} \leq 120\%$). The consequence of this is that the

Table 1
Disease characteristics

Age mean (range)	65 (46–84)
Mean PSA (range)	14.90 (1.0–77.7)
PSA group	*N (%)*
≤10	147 (41.5)
>10–20	135 (38.2)
>20	72 (20.3)
T stage	*N (%)*
<T2	64 (18.0)
T2a	71 (20.1)
T2b	60 (17.0)
T2c	66 (18.6)
T2x	1 (0.3)
T3a	62 (17.5)
T3b	29 (8.2)
T4	1 (0.3)
Gleason score	*N (%)*
<7	90 (26)
7	193 (54.5)
>7	69 (19.5)
NCCN risk group	*N (%)*
Low	9 (2.5)
Intermediate	230 (65.0)
High	115 (32.5)
Median followup	Mo (range)
Overall	59 (5–121)
20 Gy/4	103 (18–121)
18 Gy/3	67 (5–109)
19 Gy/2	21 (7–37)
16 Gy/2	40 (33–47)

PSA = prostate-specific antigen; NCCN = National Comprehensive Cancer Network.

absolute dose constraints changed, whereas the relative dose constraints remained constant.

Details on all patients were captured on a prospective database, BrachyNet. No patients were lost to followup. At each review, patients completed standard survey forms, including International Prostate Symptom Score (IPSS), rectal toxicity, and erectile dysfunction. Urethral stricture events were collected prospectively. A stricture was documented if a patient underwent a surgical procedure for a stricture (dilation or urethrotomy). This definition is equivalent to Grade 2 or higher Common Terminology Criteria for Adverse Events version 3 toxicity (9). The medical records and surgical report, when available, were used to identify the site of the stricture.

The risk of stricture was compared among the various dose groups (the dose fractionation schedule 18 Gy/3, 20 Gy/4, 19 Gy/2, or 16 Gy/2). Potential confounding factors were identified: urinary retention (defined as requiring an in-dwelling catheter within 2 weeks following the removal of the HDRB needles), previous transurethral resection of prostate (TURP), order of the treatment (HDRB before or after EBRT), the IPSS, the radiation oncologist, and the urologist. The managing urologist was included because the definition of stricture relies on a surgical procedure. This makes the definition of stricture subjective, and potentially the urologist's intervention "threshold" may influence the stricture rate.

Statistical analysis

The end point was date of first stricture. Time to stricture formation was calculated from the date of HDRB implantation. Otherwise, the date for analysis was date of last followup or date of death. Analysis was done using STATA version 8. Nelson–Aalen cumulative hazard modeling was used to estimate risk over time. The statistical significant of difference between hazard curves was calculated using the log-rank test. Univariate and multivariate analysis was performed using a Cox proportional regression model. A two-sided p-value of less than 0.05 was considered significant. Interactions between variables were tested by separately adding factors into the model. All variables in the univariate model were used for the multivariate analysis. A biologic model was also used to evaluate the total dose received by the urethra.

Results

Three hundred fifty-four patients were treated with an HDRB at William Buckland Radiotherapy Center (Table 1). The median age was 65 years. Low-, intermediate-, or high-risk nonmetastatic prostate adenocarcinoma made up respectively 2.5%, 65%, and 19.5% of patients. Forty-three patients received 20 Gy/4, 214 patients received 18 Gy/3, and 95 patients received 19 Gy/2. Two patients received 16 Gy/2 fractions as described above.

In total, 45 patients had one or more strictures: 5 in the 20 Gy/4 group (11.6%), 20 in the 18 Gy/3 group (9.3%), and 20 in the 19 Gy/2 group (21%). Neither of the two patients who received 16 Gy developed a stricture. Thirteen patients had a dilatation, whereas 32 had an urethrotomy as initial management. The actuarial risk of stricture development was 8.2% and 14% and at 24 and 48 months, respectively (Fig. 1).

Table 2 describes the number of procedures and site of stricture. Ten patients required more than one intervention, 7 had two procedures, 2 had three procedures, and 1 patient required five urethrotomies. Strictures were generally extraprostatic: 33.3% (15/45) had an apex/external sphincter stricture, 35.6% (16) had a bulbar urethral stricture, and 13.3% (6) had a membranous stricture. Only 1 patient had a prostatic urethral stricture and 1 patient had a late meatal stricture.

Dose group

The risk of stricture development was strikingly different between the dose groups (Fig. 2). The estimated cumulative risk of stricture at 2 years was 0%, 2.3%, 3.4%, and 31.6% for 16 Gy/2 ($n = 2$), 20 Gy/4, 18 Gy/3, and 19 Gy/2 patients, respectively ($p < 0.00001$, log rank).

In a univariate analysis, the 19 Gy/2 group, urologist, radiation oncologist, failed trial of void, implant year, and biologic equivalent dose (BED) all predicted for increased risk of stricture (Table 3). No significant association was seen for IPSS, order of treatment, acute urinary retention, or previous TURP. In a multivariable analysis, including all factors, the 19 Gy/2 group and implant year were two factors that remained predictive of an increased risk of stricture formation (Table 4).

Biologic urethral dose

The D_{10} (defined as the minimum dose received by the "hottest" 10% of the urethral volume) was calculated as an
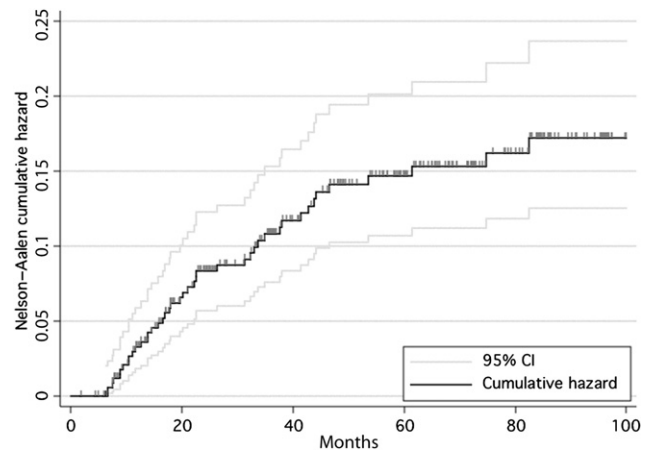

Fig. 1. Overall stricture risk over time for all patients. CI = confidence interval.

Table 2
Site and frequency of stricture seen at cystoscopy

Parameters	Frequency (%)
Number of procedures	
1	35 (77.8)
2	7 (15.6)
3	2 (4.4)
5	1 (2.2)
Documented site of stricture	
Apex/external sphincter	15 (33.3)
Bulbar urethra	16 (35.6)
Membranous urethra	6 (13.3)
Prostatic urethra	1 (2.2)
Bladder neck	2 (4.4)
Meatal urethra	1 (2.2)
Unknown	4 (8.9)

Table 3
Univariate Cox regression analysis

Factor	HR	*p*-Value	95% CI
Trial of void fail	2.1	0.034	1.1–4.1
Urologist 8	3.8	0.000	1.9–7.7
Radiation oncologist 3	2.3	0.012	1.2–4.5
Implant year 2007	7.4	0.000	3.3–16.2
Implant year 2008	3.4	0.033	1.1–10.3
BED total	1.1	0.001	1.1–1.2
20/4 Gy dose group	0.4	0.001	0.2–0.7
19/2 Gy dose group	10.9	0.000	5.0–23.7
TURP	1.37	0.42	0.6–2.9
Acute urinary retention	1.72	0.12	0.9–3.4
IPSS	0.97	0.18	0.9–1.0
HDRB before EBRT	0.83	0.60	0.4–1.7

HR = hazard ratio; CI = confidence interval; BED = biologic equivalent dose; TURP = transurethral resection of the prostate; IPSS = International Prostate Symptom Score; HDRB = high-dose-rate brachytherapy; EBRT = external beam radiation therapy.

estimated BED for 2 Gy fractions (BED_{2Gy}). This was done with an assumed α/β of 3 Gy for prostate cancer and late effects. This dose included the external beam prescribed dose (It was assumed that the urethra received the total prescribed EBRT dose). The mean urethral D_{10} (BED_{2Gy}) was 91.4 Gy in patients with a stricture compared with 87.0 Gy in those with no stricture ($p < 0.0017$, t test). However, the D_{10} (BED_{2Gy}) was significantly higher in the 19 Gy/2 dose group compared with all others (Table 5). No correlation was seen within dose groups between D_{10} and stricture risk.

Discussion

A urethral stricture is a recognized late effect of any prostate cancer therapy (10). It appears that stricture rates are higher in HDRB compared with low-dose-rate brachytherapy (LDRB) and EBRT (11), and this may imply a BED response. For example, Mohammed *et al.* (11) analyzed 1903 patients who received EBRT, LDRB, or HDRB. The stricture risk was significantly higher in HDRB patients compared with EBRT and LDRB, 11%, 2%, and 4% respectively.
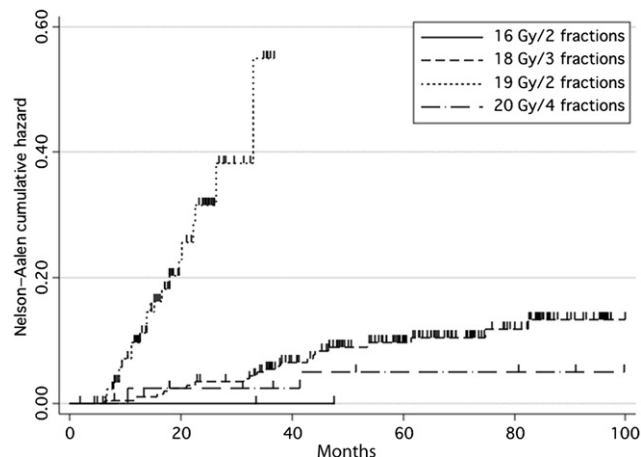
We have reported a large patient database, with prospective gathering of stricture occurrence as well as other toxicity in the followup for HDRB used as a boost to EBRT. In our patients, the overall crude stricture incidence was 12.7% and is comparable with other series (12, 13). A concerning predictive factor seen in this study was the fractionation schedule and the BED delivered to the urethra, measured by the D_{10}. The patients in the 19 Gy/2 group had a significantly higher risk of developing a stricture compared with the other fractionation schedules, and we have subsequently changed our protocol to 18 Gy/3. The D_{10} for urethra predicted stricture development, but this correlated directly to the fractionation schedule. The other predictive factor, on multivariate analysis, was a prostate-specific antigen level lower than 10 ng/mL. These patients had a significantly lower stricture rate.

This dose correlation has been reported by other groups. Sullivan *et al.* (13) reported on the late stricture risk in 474 patients treated with HDRB, either as a boost or as a monotherapy. The EBRT dose used was comparable with ours, but the HDRB schedules consisted of 16–20 Gy/4 or 19.5 Gy/3. They found a 6-year rate of 11.2% for those who received an HDRB boost to EBRT. They also reported an increased stricture rate using a high-dose single-fraction HDRB with no EBRT. In this group, the actuarial 3-year rate was 15.3%. Pellizzon *et al.* (14) reported a series of 108 men with a median followup of 4 months who received EBRT and HDRB boost of 16–20 Gy/4. At 5 years, the

Fig. 2. Stricture risk, by the dose group.

Table 4
Multivariable Cox proportional regression analysis for stricture risk

Factor	HR	*p*-Value	95% CI
Year of implant	1.2	0.041	1.0–1.5
PSA <10	0.47	0.025	0.3–0.9
19/2 Gy dose group	5.2	0.004	1.7–16.3

HR = hazard ratio; CI = confidence interval; PSA = prostate-specific antigen.

Table 5
Urethral D_{10} (BED$_{2Gy}$) for each dose group

Dose group	Mean urethral D_{10} (BED$_{2Gy}$)	Standard deviation	Frequency
18 Gy/3	82.3	1.2	206
20 Gy/4	81.5	1.2	27
19 Gy/2	100.7	1.9	95
16 Gy/2	86.2	0.8	2
Total	87.6	8.5	330

BED$_{2Gy}$ = biologic equivalent dose in 2 Gy fractions, using an α/β ratio of 3 Gy for late effects.

Note: Data are available only for 330 patients. Initial 24 patients did not have this variable documented.

actuarial stricture free rate was 86.2%. In both these series, the actuarial outcomes are comparable with ours for 18−20 Gy/3−4.

In contrast, many studies, using biologically similar schedules to ours either do not report strictures (15−18) or report only a crude rate of less than 12% (11, 13, 19−22). For example, recently Hsu *et al.* (18) reported the preliminary results of Radiation Therapy Oncology Group 0321 study. One hundred twenty-nine patients underwent a 45 Gy EBRT with an HDRB boost of 19 Gy/2. Although the followup frame is limited, they reported actuarial late genitourinary toxicity of less than 3% at 18 months. However, they neither report strictures as a separate toxicity nor is it clear that the data forms used would capture these episodes with certainty.

We were able to document the site of stricture in the vast majority of patients. Consistent with the literature, 43 of 45 strictures were at, or below, the apex. Only 1 patient had an intraprostatic stricture and 1 had a bladder neck contracture. Sullivan *et al.* (13) reported almost identical pattern of stricture positions, with 35 of 38 strictures seen in the bulbomembranous urethra. The position of strictures, at or below the apex, is suggestive of dose sensitivity in this anatomic region. In a retrospective analysis, Mohammed *et al.* (11) found that the risk of stricture was significantly associated with a bulbomembranous urethral "hotspot." In this current analysis, we have not measured dose in the bulbar/apex region. However, a higher urethral D_{10} correlated to the risk of stricture formation. Therefore, the acceptable maximum to the urethra has, as an absolute value, increased with each change in dose fractionation. If this maximal region is in the apex or bulbar region, any caudal needle movement may increase the stricture risk.

In HDRB, the potential for caudal needle movement is well documented. It is conceivable that the apex/bulbomembranous urethra is getting a higher dose owing to the needle or catheter shift. However, since September 2005, and the entire time of delivering 19 Gy/2, we have initiated prefraction CT imaging to assess caudal movement and replanning if caudal movement was greater than 1 cm. In fact, since August 2008, replanning the second fraction with CT imaging became standard. It seems unlikely that caudal needle movement has any causal relationship with strictures, given the strictures occurred when caudal movement was

less likely. However, we did not analyze the site of the urethral hot spot. Conceivably, an apical "hot" region, associated with caudal movement, is a plausible explanation for stricture formation at or below the apex.

Many other factors have been implicated in increasing the risk for urethral stricture following HDRB, yet few are consistent. A TURP before brachytherapy has been commonly associated with stricture formation in many series (13, 23−25). In this current series, there was no correlation between a stricture and previous TURP. Other clinical factors such as age, hypertension, and baseline IPSS score have been, less consistently, implicated as predictors of stricture formation (13, 14, 26).

One of the difficulties in reporting stricture rate is its very definition as a late toxicity. Using the Common Terminology Criteria for Adverse Events version 3, the definition of a stricture as an adverse event is dependent on a urological intervention, such as dilatation or urethrotomy. Different urologists may have a lower threshold to investigate and intervene in patients presenting with urological obstructive symptoms. The referral pathways and urologist involvement in followup would also influence the diagnosis of stricture. We think it is possible that the true stricture rate is underestimated owing to this definition and the practicalities of capturing these incidents.

In addition, this definition does not provide any useful grading for the severity of a stricture adverse event. A surrogate for severity may be to look at the type of procedure or the number of repeat procedures. The type of procedure used is subjective and depends on the urologist's preference and skills, rather than a true indicator of severity. Although repeat procedures are also subject to the urologist's intervention threshold, it is a reasonable marker of stricture severity. In our study, 10 (22%) patients needed a repeat procedure and of these only 3 (6.7%) needed more than two procedures. Our rate of repeat procedures is similar to other LDR and HDR series (13, 26). Many patients, who develop urethral strictures, learn self-catheterization. This procedure may impact on quality of life, more so than a one-off urethrotomy. However, we did not capture the self-catheterization rate as reliably as urethrotomy/dilatation.

Our series has captured all stricture development prospectively on an electronic database since the inception of our program, and we have high rates of sustained personal followup contact with patients. We believe that we have not therefore had any change in the likelihood of case ascertainment. We believe this increase is real, not a procedural or structural artifact. Although other factors have changed over time (specific urologist participation, replanning, and a change from steel needles to plastic catheters), we believe the multivariable analysis and consideration of biologically plausible mechanisms point to the change to 19 Gy/2 as the most likely explanation for the change we have observed. Our dose schedule, constraints, and techniques are very similar to many other groups, and it is possible that the stricture rate at higher doses per fraction is widely underappreciated because followup in

many centers is not sufficient for the frequency to become manifested, or because as discussed, the definitions and survey instruments do not reliably capture these stricture events.

Conclusion

HDRB as a boost to EBRT is a proven technique for dose escalation in prostate cancer. However, there may be a higher risk of late urethral stricture depending on the dose-fractionation schedule used. The risk for a stricture, in this large series, was most strongly related to change of the fractionation schedule to 19 Gy/2 and consequentially a higher urethral D_{10}. As it turns out, most patients diagnosed with a stricture only needed to undergo a single procedure. Brachytherapy-related urethral strictures may be underreported and may not be easily routinely captured in toxicity data. Unlike most research reports, we hope our results are not easily reproduced, and are concerned they might be, inadvertently. Our department has changed the fractionation to 18 Gy/3.

Acknowledgments

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