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REVIEW ARTICLE

Prostate cancer radiation and urethral strictures: a systematic review and meta-analysis

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Abstract

Background We performed a systematic review and meta-analysis to determine the prevalence and predictors of urethral stricture development post radiation therapy (RT) for prostate cancer (PCa).

Methods Published articles in PubMed/Medline, Cochrane, and Embase databases from January 2000 to April 2016 were queried. Inclusion criteria were any study that reported the prevalence of urethral strictures following external beam radiation therapy (EBRT), brachytherapy (BT), or both as a primary treatment for PCa. Forty-six articles met our inclusion criteria. A summary estimate of the proportion of patients who developed a urethral stricture was derived via a random effects meta-analysis.

Results In total, 16,129 PCa patients underwent either EBRT (5681, 35.2%), BT (5849, 36.3%), or both (4599, 28.5%). Overall, 630 strictures were diagnosed at follow-up with a pooled estimate period prevalence of 2.2% (95% confidence interval, CI 1.9–2.6%) in a median follow-up time of 4 years (interquartile range, IQR 2.7–5). Of which, the pooled estimate prevalence was 1.5% (95% CI 0.9–2%) post EBRT, 1.9% (95% CI 1.3–2.4%) post BT, and 4.9% (95% CI 3.8–6%) post both EBRT and BT. Of 20 studies reporting a median time to stricture formation, the overall median time was 2.2 years (IQR 1.8–2.5, range 1.4–9). In a meta-regression analysis, receiving both EBRT and BT increased the estimated difference in proportion of stricture diagnoses by 3% (95% CI 1–6%), $p = 0.018$ compared to EBRT alone. An increase in median follow-up time was found to significantly increase the risk of developing urethral strictures ($p = 0.04$).

Conclusions With a short-term follow-up, urethral strictures occur in 2.2% of men with PCa receiving radiotherapy. Receiving both EBRT and BT increased the risk of stricture formation. Longer follow-up is needed to determine the long-term natural history of stricture formation after RT.

Introduction

Worldwide, prostate cancer (PCa) is the second most common cancer in men [1]. An estimated 1.1 million men were newly diagnosed with PCa in 2012, accounting for 15% of the cancers diagnosed in men [1]. Depending on cancer risk there are a variety of treatment options for PCa including active surveillance, surgical treatment, and radiation therapy (external beam radiation therapy (EBRT), brachytherapy (BT), or both). Radiation therapy (RT) is chosen by ~25% of PCa patients in the United States (US) [2].

Although radiation planning and delivery techniques continue to improve the therapeutic ratio of cancer control to toxicity, urethral stricture remains a problematic, long-term complication [3]. RT can lead to development of

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urethral strictures by causing vascular damage, also known as obliterative endarteritis [4]. Radiation-induced strictures most often occur at the bulbomembranous junction of the urethra and significantly worsen patient quality of life by causing obstructive and irritative voiding symptoms. They are challenging reconstructive cases to manage with persistent stress urinary incontinence as a potential side effect following 28.5% of treatments [5].

The predictors and prevalence of radiation-induced urethral strictures remain unclear. Currently the literature consists of observational studies of RT complications but lacks review studies grouping the data. Given the large number of patients receiving RT, the high-cure rates for PCa and its' prolonged natural history, quality of life must be emphasized. Pooled estimates of urethral stricture following RT will allow accurate patient counseling and shared decision making. Herein, we present the first systematic review and meta-analysis on the topic. Our objective from this review was to systematically evaluate the prevalence of urethral stricture and stenosis following PCa RT and determine clinical factors associated with stricture development.

Materials and methods

Search strategy

We searched PubMed, Cochrane, and Embase databases in April 2016. The systematic literature search was done with the help of an expert information specialist (librarian) from the Medical Library, University of California, San Francisco. The search terms and search strategy can be found in Supplementary Appendix A. We followed the guidelines of the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement [6], and we registered our systematic review through (PROSPERO registration number 42016038266).

Inclusion and exclusion criteria

All study designs were included except reviews and case reports. We included studies that reported the prevalence of urethral strictures following BT, EBRT, and/or both BT + EBRT as a primary treatment for PCa. We excluded studies of adjuvant or salvage RT for cancer recurrence, studies of other PCa treatments, such as prostatectomy, cryotherapy, proton beam therapy, and high-intensity focused ultrasound therapy, studies of cancers other than the prostate, studies that grouped strictures together and did not specify the type of RT, and studies that had the same cohort. A study by Jarosek et al. was excluded due to including only urethral strictures that had procedure codes in the SEER-Medicare database, which could underestimate the true prevalence of strictures. In addition, patients from the SEER-Medicare database may coincide with patients included in other studies in our review. Figure 1 shows the flow of evidence acquisition and how we applied our inclusion and exclusion criteria. We (MAA and TWG) used covidence.com to ensure a double-blinded review to determine the included studies. Any discrepancies were discussed and resolved.

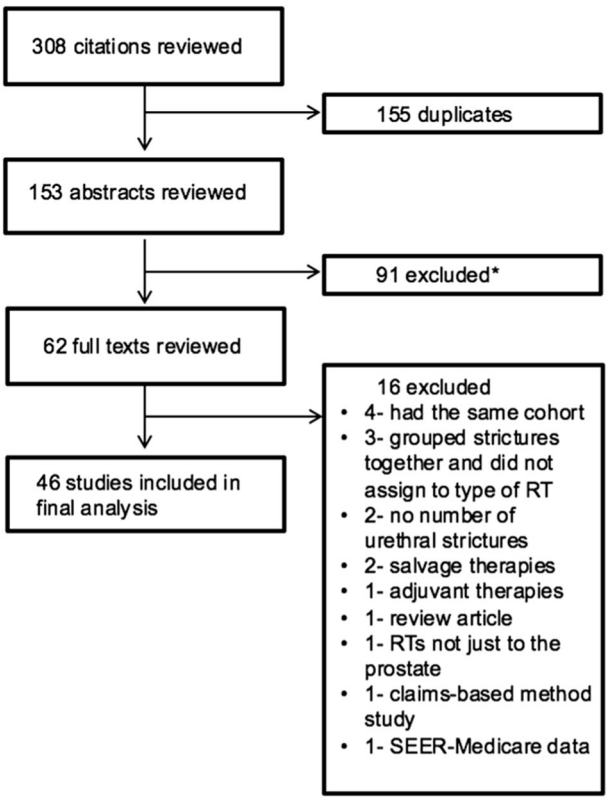

Fig. 1 Study selection flow diagram. *Exclusion from abstracts was for obvious reasons including: surgical only interventions, cryotherapy, no radiation therapy, no urethral stricture as outcome, adjuvant or salvage radiotherapies, other cancers (rectal, testicular), animal studies, other interventions, genomic studies, review articles, case reports, editorials and commentaries

Data collection and data extraction

Various study and clinical characteristics were collected from all included studies. We collected the median value preferentially but recorded the mean if the median was not reported. We collected first author names, title of studies, year of publication, location of the study (US/Canada, Europe, Asia, Australia), study design, and follow-up time (years). Clinical characteristics recorded included patient age (years), radiation type and dosage, percent of patients on androgen deprivation therapy (ADT), dosimetric parameters, history of transurethral resection of the prostate

(TURP), number of patients who developed urethral strictures, and median time to urethral stricture development. Studies were categorized into 3 groups according to the type of RT used: BT, EBRT, or BT + EBRT. If the study reported separate outcomes for urethral stricture by RT type, we recorded these observations separately. We also recorded type of BT: low-dose rate brachytherapy (LDR-BT) and high-dose rate brachytherapy (HDR-BT). We calculated the biologically equivalent dose (BED) for all studies as previously described by Stock et al.[7].

Assessment of publication bias and study quality

Since most studies were observational, we assessed the methodological quality using the Newcastle–Ottawa scale, range (0–9 stars) [8]. Because the available tests for small study bias in our situation (meta-analyses of proportion studies) are known to produce false positives [9], we used Poisson regression analysis as an alternative approach and there was no evidence of small study bias ($p = 0.59$).

Statistical analysis

The data were analyzed using STATA v14 (College Station, TX, USA). A summary estimate of the proportion of patients who developed a urethral stricture was derived via a random effects meta-analysis. Multivariate meta-regression analyses were used to determine predictors of urethral strictures following PCa RT. A sub analysis was done comparing prevalence of urethral stricture in LDR-BT and HDR-BT with and without EBRT. All tests were two-sided and a p-value of ≤0.05 was considered statistically significant.

Results

The initial search yielded 308 studies, and 46 studies met the inclusion and exclusion criteria (Fig. 1). The median quality rating for included studies was 5 stars (interquartile IQR, 4–6). A list of all studies with their characteristics can be found in the Supplementary Material (Supplementary Appendix B). In total, 16,129 PCa patients underwent either EBRT (5681, 35.2%), BT (5849, 36.3%), or both (4599, 28.5%). Most studies were done in the US or Canada (52%) and most studies were cohort studies (54%). Table 1 shows a description of the studies included in our review.

The median follow-up time for all studies was 4 years (IQR 2.6–5). The median age of patients was 68 years (IQR 65–70). Overall, 630 strictures were diagnosed at follow-up with a pooled estimate period prevalence of 2.2% (95% confidence interval, CI 1.9–2.6%) in median time follow-up of 4 years. Of which, 114 were diagnosed post-EBRT with a pooled estimate period prevalence of 1.5% (95% CI 0.9–2%) in median time follow-up of 3.2 years, 196 post-BT with a pooled estimate period prevalence of 1.9% (95% CI 1.3–2.4%) in median time follow-up of 4.2 years, and 338 post both EBRT and BT with a pooled estimate period prevalence of 4.9% (95% CI 3.8–6%) in median time follow-up of 4 years (Supplementary Appendices C, D, E). The overall median time to stricture formation was 2.2 years (IQR 1.8–2.5) in 20 studies reporting this outcome. Table 2 shows characteristics of included studies stratified by radiation type.

Table 1 Description of studies included in the review ($n = 46$)

	Studies ($n = 46$)
Total number of patients	16,129
EBRT	5681 (35.2%)
Brachytherapy	5849 (36.3%)
Both	4599 (28.5%)
Year published	
2000–2005	8 (17%)
2006–2010	17 (37%)
2011–2016	21 (46%)
Location	
US/Canada	24 (52%)
Europe	9 (20%)
Asia	7 (15%)
Australia	6 (13%)
Design	
Prospective cohort	25 (54%)
Retrospective cohort	18 (39%)
RCT	3 (7%)

Only 11 studies reported the location of urethral strictures. Majority of these strictures were at the bulbar or bulbomembranous urethra. The least common site was the meatus. Table 3 shows locations of urethral strictures in each study that reported it. Only 9 studies mentioned if patients underwent TURP before RT and specified the number of patients who underwent the procedure. Six BT studies reported dosimetric data. Supplementary Appendix F demonstrates the dosimetric parameters included in these studies.

In a multivariate meta-regression, when compared to receiving EBRT alone, receiving both EBRT and BT increased estimated difference in the proportion of stricture diagnoses by 3% (95% CI 1–6%), $p = 0.018$. An increase in median follow-up time was found to significantly increase the risk of developing urethral strictures ($p = 0.04$). Table 4 shows meta-regression analyses for predictors of urethral strictures post PCa RT. In a sub analysis of 37/46 studies that included groups undergoing BT, multivariate meta-

Table 2 Characteristics of included studies stratified by radiation type

Study characteristic	EBRT $n = 5681$ (35.2%)	Brachytherapy $n = 5849$ (36.3%)	Both $n = 4599$ (28.5%)	All groups $n = 16,129$
Number of strictures	114	196	338	630
Pooled estimate prevalence of strictures (95% CI)	1.5% (0.9–2%)	1.9% (1.3–2.4%)	4.9% (3.8–6%)	2.2% (1.9–2.6%)
Median follow-up time in years (IQR)	3.2 (2.4–5.7)	4.2 (2.7–4.8)	4 (2.8–5.1)	4 (2.6–5)
Median age in years (IQR)	69 (68–71)	66 (64–70)	66 (65–69)	68 (65–70)
Median time to stricture formation in years (IQR)	3.6 (2–3.6)	2.2 (1.8–2.4)	2.4 (1.8–2.8)	2.2 (1.8–2.5)
Median percent of patients on ADT (IQR)	59% (32–100%)	32% (17–39%)	73% (41–91%)	54% (29–84%)

Table 3 Locations of urethral strictures post radiation therapy for prostate cancer

Author	Radiation type	Total no. strictures	Bladder neck	Prostatic	Membranous	Bulbar	Penile	Meatal	Missing/ unknown
Bece	Both	19		2	16[a]			1	
Blackwell	EBRT, BT, both	58	22	4	4	23	5		
Blaivas	BT	22		22[b]					
Denham	EBRT	61		7	17	33			4
Ebara	Both	3			3[a]				
Grills	BT	8			7[a]				1
Hindson	Both	45	17	1	6	16		1	4
Makino	Both	29			27[a]				2
Merrick	EBRT, BT, both	29			29[a]				
Monroe	Both	1				1			
Sullivan	BT, both	38	2	1	35[a]				

[a]Grouped membranous and bulbo-urethral strictures together as bulbomembranous urethral strictures

[b]Did not specify whether strictures were prostatic or membranous

regression was performed comparing prevalence of urethral stricture in LDR-BT and HDR-BT with and without EBRT. No significant differences were found between the four groups (data not shown). Again, an increase in median follow-up time increased the prevalence of urethral strictures ($p = 0.009$). Median age reported, percent of patients on ADT, and BED did not show any statistically significant differences in the risk of urethral stricture development in both analyses.

Discussion

The results of this meta-analysis of 16,129 PCa patients show that the period prevalence of urethral strictures post RT is 2.2% in median follow-up time of 4 years. The pooled estimate was highest after receiving both EBRT and BT (4.9%). We also found in a multivariate meta-regression analysis that receiving combined EBRT and BT significantly increases the risk of developing urethral strictures. The median time to stricture formation was 2.2 years.

In a large review of the Cancer of the Prostate Strategic Urologic Research Endeavour (CaPSURE) multi-institutional registry, urethral strictures rates after EBRT, BT, and EBRT + BT were 1.7%, 1.8%, and 5.2%, respectively, which are similar to our review results [10]. In a more recent, large cohort, Jarosek et al. found that the 10 year incidence of urethral strictures post EBRT, BT, and EBRT + BT was 2.2, 1.8, and 1.9%, respectively. This study also found the highest incidence of urinary adverse events among RTs with EBRT + BT [11]. Furthermore, despite having an improved biochemical recurrence-free survival (b-RFS) by combining BT with EBRT [12], several studies also demonstrate an increased risk of developing urethral strictures or urinary toxicity compared to other treatment modalities [10–14].

Table 4 Meta-regression analysis for predictors of urethral strictures post prostate cancer radiotherapy

Study characteristic	Meta-regression		
	Estimated effect on proportion with stricture	95% CI	*p*-value
Radiation type			
EBRT	0	Referent	
Brachytherapy	0.01	(−0.02 to 0.04)	0.39
Both	0.03	(0.01–0.06)	0.018
Age			
Median age in years	0.001	(−0.001 to 0.002)	0.48
Follow-up time			
Years	0.005	(0.0002–0.01)	0.041
Androgen deprivation therapy			
Every 10% of patients on ADT	0.002	(−0.002 to 0.01)	0.27
10 doses increase on BED	0.0003	(−0.002 to 0.003)	0.81

CI confidence interval, *EBRT* external beam radiation therapy, *ADT* androgen deprivation therapy, *BED* biochemically equivalent dose

Interestingly in our analysis, 23 studies used HDR-BT, and 18 out of these studies used HDR-BT as a boost with EBRT. The incidence of urethral strictures post HDR-BT in published studies has been 11% [13]. Some studies suggest that the slippage or needle position changing during HDR-BT may cause urethral strictures since this position change could increase the field effect to the urethra [15]. Some centers report up to 20 mm of caudal movement of needle applicators between fractions, and this maybe the reason for having the stricture substantially inferior to the apex. This is commonly referred to as a "hot spot" area [16]. Studies have shown that decreasing the dose to the "hot spot", attention to BT-needles placement during irradiation, elimination of midline insertions, and exchanging steel needles for plastic have collectively reduced the rates of urethral strictures [13, 17].

The formation of urethral strictures is delayed after RT and the incidence of urethral stricture and stenosis will likely increase with greater follow-up [10]. Our pooled estimate median time to stricture formation was 2.2 years (IQR 1.8–2.5, range 1.4–9). Blackwell et al.[3] reported a median time to stricture formation of 3.2 years (IQR 1.3–5.3) for 38 out of 639 PCa patients after RT [3]. Thus, although the onset is variable, urethral stricture is considered a long-term complication of RT.

The latest report by the American Brachytherapy Society Task Group have demonstrated that combined modality RT have superior biochemical control in high-risk PCa than dose-escalated EBRT [18]. The report cited three randomized trials, one of which was the large ASCENDE-RT that found that combined EBRT with LDR-BT is twice as likely to be associated with b-RFS than dose-escalated EBRT alone [12]. However, this trial also showed no statistically significant differences in overall survival between the two groups. On the other hand, similar to our results, the trial has found higher prevalence of genitourinary morbidity in the LDR-BT compared to escalated EBRT. These results raise the question if it is justifiable to give combining radiotherapy to only improve b-RFS, rather than improving disease-free survival which have been found to be a surrogate for overall survival in PCa [19].

It is interesting that there was only little correlation between urethral stricture and dose to the prostate in the ASCENDE-RT [12]. Similarly, in our meta-regression analysis, the BED did not show an association with urethral stricture development. In addition, several recent studies focusing in relationship of urinary morbidity or urethral strictures with urethral dose dosimetry have failed to show a correlation between the two [20, 21]. However, we believe more dosimetric studies are needed to determine the influence on urinary morbidity. While urethral doses are determined by point dose calculations or volume, some suggest that dose differences are tolerably small and unlikely to confound the analysis of correlating urinary morbidity with urethral dosimetry [22]. For HDR-BT, some studies have shown an increased incidence of urethral stricture with higher doses per fraction [23]. In contrast, other series did not find this correlation [24, 25].

Regardless of the cause, the most common site for urethral strictures is the bulbomembranous urethra [26]. In all the studies that reported the location of urethral strictures post RT, the most common site was the bulbomembranous urethra. The reason for this is unclear, especially since this location typically receives a lower dose of radiation compared to the prostatic urethra. Bece et al.[24] suggested the possibility of having an increased radiosensitivity of the bulbomembranous urethra or it may be due to difficulty in precisely identifying the apex of the prostatic urethra by cystoscopy since the verumontanum may lie up to 1 cm within the prostate [24].

TURP alone is associated with an increased risk of urethral stricture [27]. Studies in our review have shown that history of TURPs prior to radiation significantly increases the risk of urethral strictures [23]. The likely mechanism may be due to devascularization of the urethra after TURP procedures in addition to the decreased ability of the mucosa to repair sub epithelial damage post RT [28].

It has been reported that the combination of ADT with RT improves results of high-risk PCa treatment [29]. In our multivariate meta-regression analysis, we found that the reported percent of patients on ADT was not associated with urethral strictures. However, several other series have

shown that hormonal therapy might increase the risk of developing urinary toxicity [14, 30]. Merrick et al. found a significant increase in urethral stricture rate if the duration of hormonal manipulation was more than 4 months. They suggested that this relationship could be due to a radiosensitizing effect of hormonal therapy [30]. In contrast, Elliot et al.[10] CaPSURE review was as similar to our results and found that addition of ADT did not show statistically significant differences in the rate of urethral strictures.

Limitations

One of the difficulties in reporting the prevalence of urethral stricture is that it is a very late toxicity, so studies are liable to a high rate of loss to follow-up. Most studies generally identify strictures that were severe enough to be diagnosed through investigations, therefore, there may be an underestimation of the true rates of urethral strictures development post RT. History of TURP, pretreatment urinary symptoms and dosimetry data to the urethra are major factors that could influence the prevalence of urethral strictures. These factors were not included in our analysis due to the small number of studies reporting these variables. When assessing the quality of the studies, the most common reasons for lowering the star ratings were not having a non-exposed cohort group and not reporting the rate of loss to follow-up. In addition, the heterogeneity between included studies was 84% which may raise concerns about the meaningfulness of our meta-analysis results; however, the random effects model used in our study incorporates heterogeneity in the analysis. Finally, we did not include other techniques such as targeted radiosurgery, proton beam therapy and high-intensity focused ultrasound studies due to the lack of a common dosage factor that we can calculate, such as BED for EBRT and BT. We chose to focus on the most common methods selected by men diagnosed with prostate cancer [2].

Despite these limitations, we believe this review highlights the significant effect of time on development of urethral strictures post RT, as well as the need for further follow-up to determine the true prevalence and natural history of this complication. In addition, this review will provide clinicians guidance for counseling patients about risk of prostatic stenosis or urethral stricture after RT for PCa. Many of these strictures may be misdiagnosed initially by more common diseases, such as benign prostatic hyperplasia and the true diagnosis is only reached after episodes of retention or traumatic foley catheter placements. Early detection of these strictures may decrease morbidity. Finally, future studies are warranted to explore reasons for the increased risk of urethral stricture development post EBRT + BT.

Conclusion

The occurrence of urethral strictures is 2.2% in the short-term following RT (~4 years). Receiving both EBRT and BT increased the risk of stricture formation. Longer follow-up is needed to determine the long-term natural history of stricture formation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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