The scope, presentation, and management of genitourinary complications in patients presenting with high-grade urethral complications after radiotherapy for prostate cancer

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Cite as: Doiron RC, Witten J, Rourke KF. The scope, presentation, and management of genitourinary complications in patients presenting with high-grade urethral complications after radiotherapy for prostate cancer. *Can Urol Assoc J* 2021;15(1):E6-10. http://dx.doi.org/10.5489/cuaj.6599

Published online July 17, 2020

Abstract

Introduction: The scope of complications arising after radiotherapy (RT) treatment for prostate cancer is under-recognized and not well-described. The objective of this study is to describe the presentation, scope, and management of genitourinary (GU) complications in patients referred for high-grade urethral complications or sphincter weakness incontinence after prostate RT.

Methods: A retrospective review was performed of patients referred to a reconstructive urologist for management of grade 4 urethral complications and sphincter weakness incontinence after prostate RT from December 2004 to December 2015. Patients' signs, symptoms, complications, and treatments are described.

Results: A total of 120 patients were identified, with a mean age of 67.8 years; 55.8% (n=67) received external beam radiotherapy (EBRT), 38.3% (n=46) brachytherapy (BT), and 5.8% (n=7) combination RT. The mean time to first complication after RT was 57.7 months (1–219) and number of complications per patient was 5.1±2.2. The most common associated complications were urethral stenosis (n=106, 88.3%), sphincter weakness urinary incontinence (n=55, 45.8%), radiation cystitis (n=61, 50.8%), refractory storage lower urinary tract symptoms (n=106, 88.3%), GU pain (n=28, 23.3%), and prostate necrosis/abscess (n=17, 14.2%). Patients required a mean of 7.4±4.4 treatments over a 33-month period, including urethral dilation/urethrotomy (n= 93, 77.5%), urethroplasty (n=53, 44.2%), transurethral resection (n=52, 43.3%), cystolithopaxy (n=14, 11.7%), artificial urinary sphincter (n=8, 6.7%), and urinary diversion (n=8, 6.7%). Patients with RT combined with other modalities had more complications (6.2 vs. 4.2, p=0.001), higher rates of incontinence (93.8% vs. 29.5%, p=0.001), necrosis (31.3% vs. 8.0%, p=0.003), erectile dysfunction (84.4% vs. 51.1%, p=0.001), and hematuria (59.4% vs. 36.4%, p=0.04).

Conclusions: Urethral complications related to prostate RT are seldom an isolated problem and require a substantial amount of urological resources and interventions.

Introduction

Prostate cancer is the most common non-cutaneous malignancy and is the second leading cause of cancer deaths among men in the U.S.[1] Radiotherapy (RT) is one of the most commonly employed modalities for treatment of localized prostate cancer, which in turn, has subsequently yielded a cumulatively large population of cancer survivors at risk for genitourinary (GU) complications.

The incidence of complications related to prostate cancer treatment have been described in both population-based studies and systematic reviews.[2-8] In a population-based study of 32 465 men in the province of Ontario, Nam et al[2] performed an analysis of treatment-related complications, comparing those who had undergone surgery vs. RT as primary treatment for their prostate cancer. Those who received RT had a higher five-year cumulative incidence of admission to hospital.[2] In a collaborative review of the literature, Matta et al[3] described the occurrence of seven specific pelvic complications secondary to RT, including urinary obstruction, urethral stricture, gross hematuria, rectal bleeding, ureteral stricture, rectourethral fistula, and pelvic bone complications.

Urethral complications, such as stricture/stenosis, urinary fistula, and incontinence, cumulatively represent the most common complications of RT as treatment for prostate cancer. For example, approximately 3% of men develop urinary obstruction within two years of receiving their RT,[9] while acute urinary obstruction may represent up to 25% of acute toxicity-related complications of those receiving combined modality RT.[10] The overall incidence of urethral stenosis has been reported to vary from 1–13%,[11] with a pooled incidence of 2.2% in patients receiving external beam radiotherapy (EBRT), brachytherapy (BT), or both at a median followup of four years.[12] The relative incidence between modalities was 1.5% following EBRT, 1.9% post-BT, and 4.9% in those receiving combined modality RT.

Other complications, such as gross hematuria, rectal bleeding due to proctitis, osteomyelitis, and secondary

malignancies, are reported to arise following RT as treatment for prostate cancer. Their incidences, like several pelvic complications experienced following RT, tend to increase over time. Incidence rates vary depending on dosage and modality of RT received.[13-16]

Despite these studies, the exact clinical scope of complications at a patient level and their management remains poorly understood. We aimed to describe the clinical scope and management of urethral complications secondary to RT treatment of prostate cancer. Our hypothesis is that these complications are seldom isolated entities and, thus, require multiple treatments.

Methods

We retrospectively reviewed patients presenting or referred to a single reconstructive urologist for management of Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) morbidity score[17] grade 4 urethral complication of prostate RT or sphincter weakness urinary incontinence secondary to prostate RT over an 11-year period (December 2004 to December 2015). Inclusion criteria included any patient presenting or referred to a single reconstructive urologist for treatment of grade 4 urethral complications (defined as urethral stricture/stenosis or fistula) or sphincter weakness incontinence secondary to RT as a curative treatment for prostate cancer, whether in the form of EBRT, BT, or both. Only patients presenting with urethral stricture/stenoses confirmed to be de novo, post-RT stricture/stenoses were included in the cohort. Patients with radiation treatment for non-prostate cancer-related diagnoses were not included in the analysis.

Patient demographics, presenting signs and symptoms, GU complications, and interventions received as treatment of their symptoms or complications are described. Alberta's medical record system is province-wide and, thus, information related to prior prostate cancer treatment, GU complications related to RT, and associated interventions were easily accessible. For patients referred from outside the province, records were obtained from the referring physician.

Urethral stricture was defined as either de novo bulbomembranous strictures or posterior urethral stenosis that are typical of those associated with RT. Urinary tract infection (UTI) was defined as a positive urine culture with symptoms consistent with UTI. Radiation cystitis was defined as significant if the patient was symptomatic and required urological intervention. Acute urinary retention (AUR) was defined as patients requiring emergent urological intervention. Likewise, hematuria was defined as hematuria requiring urological intervention. Urological intervention in these cases were defined as placement of a urethral or suprapubic catheter, cystoscopy, urethral dilation over guidewire, or bladder irrigation. Prostate necrosis or abscess was diagnosed on either cystoscopy or identified on imaging. Refractory storage lower urinary tract symptoms (LUTS) were those patients experiencing persisting storage symptoms despite alleviating obstruction and failing anticholinergic therapy, while erectile dysfunction (ED) was patient-reported and refractory to primary care management. Major urethral surgery was defined as requiring urethroplasty, insertion of an artificial urinary sphincter (AUS), or fistula repair.

Single-modality RT group consisted of those who received either EBRT only or BT only, while the combined group were those receiving RT combined with other treatments, such as radical prostatectomy, cryotherapy, or additional RT. Descriptive statistics, Chi-squared test, and Student t-tests were used to summarize and compare clinical findings.

Results

A total of 120 patients were identified and included in the analysis, with cohort demographics outlined in Table 1. Average patient age was 67.8±8.3 years, with a mean time from RT treatment to GU complication of 57.7 months. In terms of RT modality, most patients received EBRT alone (n=67, 55.8%), while 46 patients (38.3%) received BT alone. A total of seven patients (5.8%) received both EBRT and BT. Twenty-one patients (17.5%) had previously undergone radical prostatectomy.

Patients experienced a mean of 5.1±2.2 complications secondary to their RT (Table 2). The most common associated sign, symptom, or complication was urethral stricture/stenosis or refractory storage LUTS persisting despite treatment, each found in 106 (88.3%) patients, respectively. Other frequently reported complications included ED in 72 (60.0%) patients, radiation cystitis in 61 (50.8%) patients, AUR in 60 (50.0%) patients, sphincter weakness urinary incontinence in 55 (45.8%) patients, and gross hematuria in 51 (42.5%)

Table 1. Demographics of the patient cohort

Factor	n (%)
Number of patients	120
Patient age (years)	67.8±8.3 (49–84)
Mean time to complications from radiotherapy (months)	57.7±54.5 (1–219)
Radiotherapy modality	
BT	46 (38.3%)
EBRT	67 (55.8%)
Combined RT	7 (5.8%)
Prior radical prostatectomy	21 (17.5%)
Salvage cryotherapy	4 (3.3%)
Mean number of lower tract complications	5.1±2.2 (1–12)
Stenosis length (cm)	2.5±1.5 (1–9)

BT: brachytherapy; EBRT: external beam radiotherapy; RT: radiotherapy.

Table 2. Signs, symptoms, and complications associated with high-grade urethral toxicity after radiotherapy

Sign, symptom, associated complication	Presenting complaint (n=120)	Reported as secondary sign/ symptom/ complication
Urethral stricture/stenosis	97/120 (80.8%)	106/120 (88.3%)
Sphincter weakness urinary incontinence	9 (7.5%)	55 (45.8%)
ED	–	72 (60.0%)
GU pain	1 (0.8%)	28 (23.3%)
UTI	–	27 (22.5%)
Radiation cystitis (symptomatic)	8 (6.7%)	61 (50.8%)
AUR	–	60 (50.0%)
Hematuria	–	51 (42.5%)
Prostate necrosis/abscess	–	17 (14.2%)
Pubic osteomyelitis/ prostatosymphyseal fistula	2 (1.7%)	4 (3.3%)
Refractory storage LUTS (independent of stricture treatment)	2 (1.7%)	106 (88.3%)
Rectourethral fistula	1 (0.8%)	1 (0.8%)
De novo cancer (bladder or rectum)	–	7 (5.8%)

AUR: acute urinary retention; ED: erectile dysfunction; GU: genitourinary; LUTS: lower urinary tract symptoms; UTI: urinary tract infection.

Table 3. Overall management of radiotherapy complications

	n (%)
Mean number of therapeutic procedures per patient	7.4±4.4 (1–30)
Treatment followup (months)	33.3±26.9 (1–116)
Procedures required by patients	
Major urethral surgery	59/120 (49.2%)
Urethral dilation/urethrotomy	93 (77.5%)
Urethroplasty	53 (44.2%)
AUS	8 (6.7%)
Transurethral resection (prostate, bladder neck, bladder tumor, clot evacuation)	52 (43.3%)
Cystolithopaxy for lower tract calculus	14 (11.7%)
Long-term suprapubic catheter	16 (13.3%)
Urinary diversion	8 (6.7%)
Deemed poor reconstructive candidate	46 (38.3%)

AUS: artificial urinary sphincter.

patients. A total of 28 (23.3%) patients reported GU pain following their RT treatment, while 27 (22.5%) patients reported a history of UTI following RT. Other less common but severe complications included prostate necrosis/abscess in 17 (14.2%) patients, de novo cancer in seven (5.8%) patients, and pubic osteomyelitis/prostatosymphyseal fistula in four (3.3%) patients.

Patients typically required multiple procedures for treatment of their complications, with a reported mean number of 7.4±4.4 therapeutic procedures received per patient over a mean treatment interval of 33.3 months (Table 3). Fifty-nine patients (49.2%) required major urethral surgery, defined as either urethroplasty, repair of fistula, or implantation of an AUS. A total of 93 (77.5%) patients underwent urethral dilation or urethrotomy as part of their treatment. Urethroplasty was required in 53 (44.2%) patients, while eight (6.7%) patients eventually received surgical treatment of their sphincter weakness urinary incontinence. Transurethral resection was carried out in 52 patients (43.3%) for a variety of indications, including transurethral resection of prostate, bladder neck, or bladder tumor or clot evacuation. Cystolithopaxy and transurethral extraction of a lower urinary tract stone was required in 14 patients (11.7%). Placement of a suprapubic catheter for potential long-term urinary drainage was required in 16 patients (13.3%), while urinary diversion was performed in eight patients (6.7%).

Patients undergoing treatment with RT combined with other modalities (Table 4), such as radical prostatectomy, cryotherapy, or combination RT, had more complications (6.2 vs. 4.7, p=0.001) and were more likely to have incontinence (93.8% vs. 29.5%, p<0.001), necrosis or abscess (31.3% vs. 8.0%, p=0.003), ED (84.4% vs. 51.1%, p=0.001), hematuria requiring intervention (59.4% vs. 36.4%, p=0.04), and trended toward requiring more procedures (10.1 vs. 7.2, p=0.08).

Discussion

This retrospective, single-surgeon case series of patients presenting for treatment of urethral complications and sphincter weakness incontinence secondary to RT for prostate cancer treatment describes the clinical scope of high-grade GU complications attributable to pelvic RT treatment and their overall management. The scope of GU complications was broad-ranging, from urethral stenosis, UTI and refractory LUTS to more devastating complications, such as prostatic necrosis, abscess, and rectourethral fistula. Multiple complications were the norm, with patients presenting with a mean of 5.1 complications and typically in a delayed fashion at a mean of 57.7 months after treatment. This further confirms that radiation complications typically present late and increase in a time-dependent manner.[5,6] This finding also emphasizes the need for long-term survivorship care in patients undergoing prostate RT.

The typical multiplicity of RT complications poses a significant therapeutic challenge. The sheer spectrum of symptoms and complications renders a standardized treatment approach challenging. The majority of patients (88.3%) had urethral stenosis but coexistent high rates of incontinence (45.8%), ED (60.0%), radiation cystitis (50.8%), and GU pain (23.3%), which make treatment more challenging than simply addressing an isolated urethral stenosis.

This study also simultaneously provides a comprehensive description of the management of RT complications and

Table 4. The effect of radiotherapy combined with other treatment modalities (cryotherapy, radical prostatectomy, second radiation)

Complication	Combined modalities n (%)	Isolated radiotherapy n (%)	p
Mean number of complications	6.2±2.7	4.7±1.8	p=0.001*
Urethral stenosis/stricture/ contracture	25/32 (78.1%)	81/88 (92.0%)	p=0.06
Incontinence	30 (93.8%)	26 (29.5%)	p<0.001*
De novo cancer (rectal or bladder)	3 (9.4%)	4 (4.5%)	p=0.38
Pubic osteomyelitis/ prostatosymphyseal fistula	3 (9.4%)	1(1.1%)	p=0.06
Prostate necrosis/abscess	10 (31.3%)	7 (8.0%)	p=0.003*
Radiation cystitis	21 (65.6%)	40 (45.5%)	p=0.06
Radiation proctitis	13 (40.6%)	14 (15.9%)	p=0.006*
Erectile dysfunction	27 (84.4%)	45 (51.1%)	p=0.001*
Genitourinary pain	11 (34.4%)	17 (19.3%)	p=0.09
Urinary tract infection	7 (21.9%)	20 (22.7%)	p=1.0
Hematuria	19 (59.4%)	32 (36.4%)	p=0.04*
Acute urinary retention	16 (50.0%)	33 (50.0%)	p=1.0
Refractory storage LUTS	25 (78.1%)	81 (92.0%)	p=0.05*
Mean number of procedures	10.1±4.5	7.2±4.3	p=0.08
Poor reconstructive candidate	15 (46.9%)	31 (35.2%)	p=0.25

*Statistically significant. LUTS: lower urinary tract symptoms.

reveals that patients suffering complications often require multiple therapeutic procedures. The average burden of intervention was high; patients received a mean of 7.4 therapeutic procedures as management of their GU complications over 33 months, with almost half — 49.2% — requiring major reconstructive urethral surgery, defined as urethroplasty, urethral fistula repair, or implantation of an AUS. The number of patients undergoing reconstructive surgery would likely be higher, however, 38.3% were deemed poor reconstructive candidates due to the multiplicity of their problems, limiting the number of effective treatment options as determined by the treating reconstructive urologist (KFR). This contributed to the large number of temporizing procedures required over a relatively short treatment period after presenting for treatment. Patients require a broad range of treatments, with high rates of endoscopic procedures for stricture, hematuria, lower urinary tract calculi, or secondary malignancy. Ultimately 1/5th or more of patients required urinary diversion, either in the form of formal urinary diversion or an indwelling suprapubic catheter.

Given the broad scope and therapeutic intensity of RT complications, the incidence with which they occur is of utmost importance. In a population-based study of 32 465 men in the province of Ontario, Nam et al[2] performed a comprehensive analysis of treatment-related complications, comparing those who had undergone surgery vs. RT as primary treatment for their prostate cancer. In their analysis, they focused on complications other than urinary incontinence and erectile function. Of the 32 465 men who received treatment for prostate cancer over the study period, 16 595 received RT. Those who received RT as had a higher five-year cumulative incidence of admission to hospital (hazard ratio [HR] 10.8, 95% confidence interval [CI] 9.04–12.9, p<0.0001), requiring a rectal or anal procedure (HR 2.72, 95% CI 2.40–3.08, p<0.0001), developing a secondary malignancy (HR 2.08, 95% CI 1.48–2.91, p<0.0001), and requiring an open surgical procedure (HR 3.68, 95% CI 2.16–6.26, p<0.0001). Almost uniformly, the incidence of complications was higher for men undergoing RT when compared to radical prostatectomy. This appears true for other associated complications, with an increase in their incidence over time. Studies have suggested an 8–18% 10-year cumulative incidence of gross hematuria,[13,14] while the incidence of rectal bleeding has ranged from 4–6% in published studies.[15,16] Likewise, the rate of fistulae involving the gastrointestinal tract and risk of developing a secondary malignancy increases with time.[2,17]

Thus, GU complications following RT as treatment of prostate cancer, as described in population-based studies, demonstrate an increased rate in the incidence of individual complications when compared to surgery but lack granular data and excludes some of the more common or more devastating complications included in the current analysis, such as refractory LUTS, ED, UTI, necrosis, and fistulae.[3] Moreover, population-based studies are mostly limited to describing the first complication experienced by patients requiring hospitalization[2,5] and the scope of complications reported is limited due to the nature of their data set. However, the cumulative incidence of RT complications, as described in population-based studies, when combined with our current series describing complications at a patient level reveal the typical scenario is that multiple complications are the norm and patients require frequent and/or intense surgical interventions; this supports the suggestion that RT is possibly a more morbid treatment of prostate cancer when compared to radical prostatectomy in the long-term.

There are some limitations to the current study that warrant discussion. Firstly, the RT received is not described in terms of primary vs. salvage vs. palliative, and other relevant RT parameters are lacking. The patient population, therefore, may represent a heterogeneous group in terms of extent of disease and overall dosage of RT received. We suggest, however, that including salvage and palliative patients, where typically lower doses of RT would be provided, if anything might underestimate the degree of complications. Additionally, the authors did not include data regarding neoadjuvant, adjuvant, or salvage androgen deprivation therapy (ADT). It is possible that ADT may have contributed in some

way to specific GU complaints, although we suspect, given the list of treated GU complications, its contribution would have been minimal and largely limited to ED.

The limitations inherent in descriptions of case series are recognized. The described surgeon is a high-volume reconstructive urologist with a large referral base working in a tertiary academic institution. The patient population presented here may, therefore, not be representative of community practice and patients may be overly representative of more complex presentations of their GU complications.

Furthermore, there is no way to determine the incidence of complications from the current study, as we are reporting on a case series of patients referred with GU complications following prostate cancer treatment with RT. In terms of the complications described, although patients attributed their complications to their RT treatment, the authors acknowledge that some of the described complications, including refractory LUTS, AUR, and ED, can be multifactorial and may not be directly related to RT. Also, with a mean intervention burden of >7 procedures per patient, the authors recognize that some of these interventions may represent re-intervention for the same complication, e.g., multiple transurethral resections of bladder tumor for de novo bladder cancer. Regardless of re-intervention or not, >7 procedures per patient is meaningful and even if re-interventions were excluded, we would still expect to see a significant burden of intervention for management of these complications.

Despite these limitations, the current study provides a more in-depth analysis of the scope of complications that may be attributable to RT treatment of prostate cancer than we have observed in the literature to date. It builds on previous publications exploring this emerging trend and may further enable patients to make informed decisions regarding therapy for prostate cancer, while practitioners may be better equipped to counsel those considering prostate cancer treatment.

Conclusions

Patients receiving RT as treatment for their prostate cancer experience a broad scope of complications, seldom in isolation and often requiring multiple interventions for their management.

Competing interests: Dr. Rourke has been an advisory board member for and is a shareholder in Boston Scientific; and has participated in clinical trials supported by Red Leaf Medical. The remaining authors report no competing personal or financial interests related to this work.

This paper has been peer-reviewed.

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