Evaluation and management of urinary retention after pelvic radiation therapy

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Abstract: Pelvic radiotherapy for the treatment of malignancy is known to cause unintended urinary toxicity including urinary retention and urethral stricture disease (USD). In the treatment of prostate cancer with radiotherapy, the reported rate of USD is between 1.7–5.2% while urinary toxicity has been reported in as high as 16% of patients that undergo radiotherapy for the treatment of rectal cancer. The purpose of this review article is to evaluate literature regarding the role of pelvic radiotherapy in causing urinary retention and to discuss the unique treatment considerations for urinary retention in the irradiated man ranging from urinary catheter placement to transurethral dilation (UD) to open surgical repair.

Keywords: Radiation; urinary retention; urethral stricture

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Introduction

The utilization of radiation therapy (RT) in the treatment of malignancy has advanced rapidly since the discovery of X-rays by German physicist Wilhelm Röntgen in 1895 (1). The first reported clinical use of RT as treatment of disease was by Grubbé *et al.* in 1896 in Chicago, IL when he used X-ray to treat advanced ulcerated breast cancer (2). RT's natural radioactivity was discovered mere months later by French physicist Henry Becquerel and over the last century, there has been considerable progress made in refining the mechanism of tissue-specific targeting to maximize tumor killing while minimizing unwanted side effects.

Bladder, prostate, and colorectal cancers are estimated to account for approximately 332,200 new cancer diagnoses in men in the United States in the year 2020 alone (3). Pelvic radiation has a significant therapeutic role in the treatment of these cancers, including intermediate and high-risk prostate cancers, recurrence after radical prostatectomy, muscle-invasive bladder cancer and others (4,5). Pelvic RT used in the treatment of these cancers is delivered either interstitially via brachytherapy (BT), where small radioactive pellets are placed directly into the tissue of concern providing localized radiation, externally via external beam radiation therapy (EBRT), or a combination of both BT and EBRT. Despite advancements in the radiation delivery technology over the last 100 years, this therapy modality still carries a notable risk of damaging surrounding normal urinary tract tissue and warrants sustained follow-up to ensure optimized care of these patients.

Therapeutic RT is known to promote cellular senescence, thereby halting the growth of cancer cells within malignant tissue (6). RT is posited to damage normal tissue in the more immediate setting by both depleting stores of stem cells and progenitor cells as well as disrupting vascular endothelial microvessels leading to a type of obliterative endarteritis (7). Progressive future damage from RT is thought to be mediated by inhibition of repopulation of stromal stem cells by long-lived free radicals, reactive oxygen species, and proinflammatory cytokines/chemokines leading to greater cell loss, tissue damage, fibrosis, necrosis, and functional tissue deficits (8,9). Urethral stricture in the anterior urethra is caused by the corpus spongiosum being slowly replaced with fibrosis that subsequently occludes the urethral lumen, while posterior urethral stenosis is more commonly caused by trauma or surgical treatment (10). The location and severity of urethral occlusion may result in urinary retention. This narrative review of the literature was conducted utilizing the free online search engine PubMed with a focus of exploring pelvic RT as a known risk factor for urinary retention through its ability to cause urethral stricture formation and bladder neck stenosis.

Etiology

Acute urinary retention (AUR) occurring in radiated men within 12 months of RT is thought to be mediated by an edematous inflammatory response that occurs initially during RT. While this may resolve in the short term as inflammation subsides, in some cases it persists longer than 12 months as persistent urinary retention (PUR). It is important to distinguish AUR from PUR as this has an impact on the acuity, prognosis, and treatment strategy.

In some cases, AUR may be attributable to preexisting bladder outlet obstruction (BOO), such as benign prostatic hyperplasia (BPH), that previously went unrecognized or untreated and subsequently became exacerbated by the initial inflammatory response seen during pelvic radiation. Chronically, PUR could be due to development of an anatomic obstruction like anterior urethral stricture or posterior urethral stenosis after RT. Another cause of urinary retention is detrusor underactivity, where no anatomic or functional obstruction to the bladder exists, but rather poor emptying occurs due to an insufficient bladder contraction. While further investigation is required to properly delineate the relationship between an irradiated bladder and the subsequent development of AUR, there are many studies that indicate that higher doses of bladder RT predispose patients to urinary toxicity, including AUR (11-13).

Incidence

Urethral strictures following radiation treatments for prostate cancer occur in the bulbomembranous portion of the urethra >90% of the time (14-17). A recent review of the CaPSURE database by Nicholson found that the incidence of urethral stricture following RT for prostate cancer can be between 1.7–5.2% at a median follow-up of 2.7 years. They noted that the risk of urethral stricture disease (USD) by treatment regimen in descending order was EBRT+BT (5.2–16%), followed by BT alone (1.8% in primary setting, 7.5% in salvage setting), and then EBRT alone (1–13% in primary setting, 3–8.5% in salvage setting) (15).

While the literature surrounding the relationship of RT in the treatment of colorectal cancer and urinary morbidity is sparse, a study by Kwaan and colleagues using SEER data evaluated the rate of adverse urinary events in over 11,000 rectal cancer patients, and they found that, overall, 16.7% of rectal patients experienced an adverse urinary event (18). Urinary retention was the most common side effect and occurred in 8% of patients undergoing surgery and preop EBRT and in 10.4% of patients undergoing surgery and postop-RT. Patients who underwent radiation preoperatively or postoperatively had an adjusted hazard ratio for adverse urinary events of 2.24 (95% CI, 1.79–2.80) and 2.04 (95% CI, 1.70–12.44), respectively. Another study by Pollack and colleagues reported that preoperative RT before surgical management of rectal cancer led to significantly more late urinary complications, including urinary incontinence in 45% of those who underwent preoperative RT *vs.* 27% in those that did not (P=0.023) (19). A Dutch study found no significant differences in voiding problems between those that underwent preoperative RT before total mesorectal excision and those that did not (20).

With regards to bladder cancer, RT is rarely utilized adjunctly with cystectomy. Instead, it is a component of a tri-modality therapy in which the patient undergoes maximal transurethral resection of the bladder tumor (TURBT), followed by chemotherapy and EBRT. There are known increases in late urinary toxicity following RT in trimodality therapy; however, little is reported on the incidence of urethral stricture or urinary retention in this particular population given its less common use.

Workup

When evaluating a patient with obstructive symptoms following pelvic radiation, the first step is obtaining a detailed and thorough clinical history, including his or her past medical and surgical history, social history, and current medications (21). Many medications contain anticholinergic effects and are known to precipitate urinary retention; thus, a reconciliation of all medications should be completed during the visit (22). Next, it is vital to ascertain the type and stage of their cancer and the duration of pelvic RT as each is treated differently. In addition, assessing for any pre-existing obstructive urinary symptoms concerning for existing urinary retention prior to RT is necessary to separate RT-induced AUR from iatrogenic or traumatic causes of AUR/PUR. The severity of symptoms is quantified via the International Prostate Scoring System (IPSS), where patients are able to rate the severity of obstructive/irritative urinary symptoms and its effect on their quality of life (23). Once the history has been obtained, a focused physical examination of the genital, abdominal, pelvic, and neurologic systems should be obtained. Urinalysis and urine culture are often obtained as adjunct laboratory tests to rule out urinary tract infections as a reversible, organic cause of obstructive/irritative symptoms. A post-void residual (PVR) is important to evaluate for incomplete bladder emptying (24). The complex patient may also require cystoscopy to visually evaluate their anatomy, or urodynamic testing to investigate bladder compliance, capacity, sensation to void, and voiding function. Commonly used imaging modalities may include voiding cystourethrogram, retrograde urethrogram (RUG), CT abdomen/pelvis, MRI, or ultrasound (25). For the sake of completeness, it is important to note that EBRT to the pelvis is a known risk factor for development of bladder cancer, and thus patients with either gross or microscopic hematuria should be evaluated further (26).

Management

A critical first step in management of a patient with urinary retention is ruling out a functional or anatomic obstruction. For patients with AUR without obstruction on imaging, cystoscopy, or urodynamics, bladder decompression via foley catheter placement is paramount. In some cases, a period of bladder decompression followed by a trial of void may allow for spontaneous voiding and no further intervention. In patients with persistent, symptomatic retention, clean intermittent catheterization is a preferred method for management. Additionally, studies have reported success of alpha blockers (i.e., tamsulosin) in the management of urinary retention, and they should be utilized as an adjunct therapy along with bladder decompression to promote successful spontaneous voiding following initial decompression (27).

BPH

In patients with BPH and/or BOO, surgical options can be considered based on a man's quality of life, degree of bother from symptoms, and candidacy to undergo surgery. There are a multitude of ways to resect the prostate, with transurethral resection of the prostate (TURP) being considered the gold standard (28). Other endoscopic means to treat BPH include laser enucleation/resection using holmium laser (HoLEP/HoLRP) or thulium laser (TmLEP/TmLRP), as well as photoselective "green light" vaporization of the prostate (PVP), and transurethral vaporization of prostate (TUVP). Prostatic urethral lifts (UroLift) have also been used for the treatment of BPH with reported improvement of AUA Symptom Index up to 11 points with stable reduction in symptoms for as long as 5 years after placement (29,30). It is important to note that all of these surgical modalities themselves carry the risk of future USD and bladder neck stenosis that can consequently cause urinary retention (31). This risk is in part due to the optical dilation from the larger sheath of a resectoscope, the intraurethral manipulation to accomplish the surgery, and the electrosurgery used in the resections themselves.

One must be wary of using energy modalities on the prostate after radiation as the risk of a transurethral prostate procedure in the radiated patient includes devastating complications like rectourethral fistula and pubic symphysis fistula/osteomyelitis (*Figure 1*) (32-34).

While historically patients with localized prostate cancer and LUTS were considered poor candidates for BT because of a theoretical risk of postoperative urinary mortality including urinary retention (35), many recent studies have challenged this idea. A study of 38 patients that underwent limited TURP six months after I-125 BT for localized prostate cancer with LUTS by Liu and colleagues showed statistically significant improvement in mean IPSS, quality of life score, peak flow rate, and PVR, with no patients developing urinary retention, urethral necrosis, or urinary incontinence at mean follow-up of 32 months (36). Alternatively, Ivanowicz and colleagues report that the use of transurethral procedures such as TURP/TUIP can be a safe and effective treatment strategy in men with LUTS and low to intermediate prostate cancer when the TURP/TUIP is planned more than four months before BT (37). In their study of 42 patients with median follow up of 39 months, no patients developed retention, urethral necrosis, or urinary incontinence. Additionally, an analysis of 2,000 patients from the St. Luke's Cancer Centre database, Brousil and team found that in patients at increased risk of voiding symptoms including urinary retention, low dose rate BT is not contraindicated if the patient received a modified

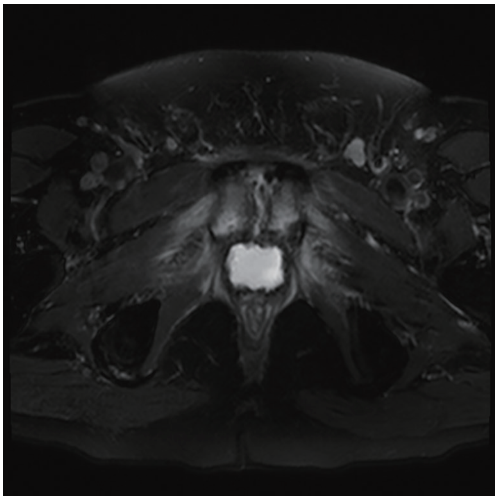

Figure 1 Axial MRI showing urethrapubic fistula.

Figure 2 Axial CT of the pelvis with calcified prostatic fossa.

TURP prior (median 64 days) to BT seed implantation (38).

In patients with obstructive symptoms, Peigne's group suggested that PVP completed at least 6 weeks prior to prostate BT was safe and technically feasible (39). Nonetheless, the use of PVP in previously irradiated patients has not been well studied. Some studies suggest comparable treatment of prostatic obstruction after BT or EBRT with either PVP or TURP (40). No and colleagues published a study of 12 patients that underwent PVP after previous RT (6 EBRT, 6 BT) and found a durable response with PVP while maintaining continence in those with lower urinary tract symptoms (LUTS) or retention (41).

In our practice we have also routinely seen patients with a calcified/necrotic prostatic fossa after undergoing pelvic radiation followed by an outlet obstruction procedure (*Figure 2*), usually PVP or after repetitive TUR

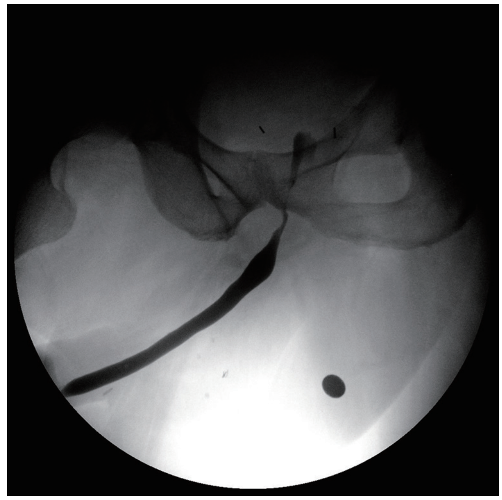

Figure 3 Retrograde urethrogram with evidence of membranous urethral stenosis after EBRT for prostate cancer. EBRT, external beam radiation therapy.

procedures at the bladder neck. Notably, these patients often have recalcitrant perineal and pelvic pain marked by incontinence, hematuria, and recurrent cystitis.

Stricture management

For patients who develop anatomic obstruction via urethral stricture after pelvic radiation, it is critical to delineate the anatomic location of the obstruction along the urethra as subsequent surgical interventions may be approached perineally or abdominally depending on the stricture/stenosis location. Commonly encountered locations include the anterior urethra, membranous urethra (*Figure 3*), or prostatic urethra/bladder neck (*Figure 4*).

Most radiation-induced urethral strictures form at the bulbomembranous urethra and have an increase in incidence over time (15,42). Effective management consists of endoscopic procedures and open surgical options. Endoscopic options include urethral dilation (UD) and direct visual internal urethrotomy (DVIU). Unfortunately, these have been associated with a urethral stricture recurrence rate of about 50% within 16 to 60 months (43).

Recurrent bladder neck contractures (BNC) are often managed effectively with deep lateral transurethral incision of bladder neck contracture (TUIBNC). Ramirez and colleagues reported their 5-year experience with TUIBNC and found that after TUIBNC, 72% required no further surgery for obstruction at a mean follow up of 12.9 months

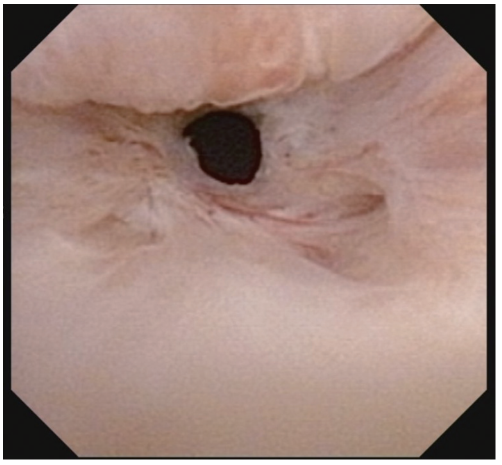

Figure 4 Cystoscopic view of bladder neck stenosis after radiation for prostate cancer.

and reported an overall success rate of 86% after two procedures (44). Significant factors associated with treatment failure were >10 pack/year smoking history and ≥2 previous endoscopic BNC procedures. However, since only two of their patients had previously undergone pelvic RT, no conclusions could be made regarding the association of previous pelvic RT and TUIBNC success.

In addition to transurethral incision (TI) of stenotic portions of the urethra, transurethral resection (TR) is also used. A study by Pfalzgraf of 103 patients undergoing endoscopic treatment for vesico-urethral anastomotic stricture with either TI or TU found that a history of radiation prior to TI or TR was not a statistically significant contributor to treatment success or post-operative *de novo* urinary incontinence (45).

In addition to standard urethral procedures mentioned above, adjuncts medications are often used to prevent recurrence of stricture after endoscopic management. These include a local injection of steroids or mitomycin-C (MMC). Vanni *et al.* reported 72% patency after 1 procedure and 89% patency after two procedures when administering intralesional MMC along with urethrotomy (46). Two groups have reported their experience with the use of intralesional steroid (triamcinolone) injection during TI. Eltahawy and colleagues reported a success rate of 70.8% for a single treatment and 83% for two treatments of holmium laser bladder neck incision and triamcinolone injection for anastomotic stenosis after radical prostatectomy in 24 patients (47). Mann and colleagues report very similar results with 70.0% recurrence-free rate after a single treatment and 83.3% recurrence-free rate after TI with concomitant intralesional triamcinolone administration in 30 patients (48). Both cohorts included only five patients with previous RT. Mann reported that all five previously irradiated patients had their recurrent BNC successfully treated with a single treatment of TI with intralesional steroid injection while one of the five previously irradiated patients in the Eltahawy study required suprapubic tube placement after two failed attempts of TI with intralesional steroid injection.

Management of USD with chronic suprapubic tube prior to surgical repair is reported to allow for more accurate assessment of stricture severity and involvement and aid in surgical planning by allowing urethral tissue recovery without the need for urethral catheterization or manipulation (49,50). Additionally, In appropriately counseled patients who fail endoscopic management and are not a candidate or do not desire a more invasive operation, placement of a suprapubic tube for long term urinary diversion is an appropriate treatment option.

Some of the more invasive surgical options for managing strictures are excision and primary anastomosis (EPA), where the diseased portion of the urethra is removed and the healthy proximal and distal margins are sewn together, as well as dorsal onlay urethroplasty with buccal mucosal graft (BMG), where the strictured portion of urethra is opened and oral mucosa is sewn over the defect. In a multicenter study by Hofer and colleagues, 66 of 72 men with radiation-induced urethral strictures were treated with EPA (51). Successful reconstruction was achieved in 46/66 patients (69.7%) with a mean time to recurrence of 10.2 months. New onset incontinence occurred in 12 patients (18.5%); however, the new onset of incontinence was associated with a stricture length greater than 2 cm.

Glass and colleagues also reported their outcomes on various forms of urethroplasty for 29 men with radiation-induced urethral strictures. EPA was performed in 22/29 (76%) of patients, followed by BMG in 5/29 (17%), and perineal flap repair in 2/29 (7%). The success rate was found to be ~90% at a median follow-up time of 40 months. The incidence of incontinence was noted to be 2/29 (7%) (52).

In a multi-institutional study of 79 men with post-radiation posterior urethral stenosis, Policastro and colleagues found that dorsal-onlay BMG urethroplasty was a safe and feasible reconstructive technique with 96.6% continence rate and 17.7% stricture recurrence rate (53). Contrary to classical teaching, this study helps reinforce the notion that BMG can survive in a radiated field.

Surgical management of radiation-induced urethral strictures and bladder neck stenosis have typically taken an open approach. However, just as urologic oncology has become more minimally invasive—so has urologic reconstruction. In a study by Sun and colleagues, 4 patients with radiation-induced posterior urethral strictures underwent robotic posterior urethroplasty. All patients were discharged on post-operative day 1 without any complications or conversions to open surgery. Additionally, the operation was successful in all patients with no evidence of recurrence at median follow up on post-operative day 124 (54). Zhao and colleagues have reported robotic assisted Y-V plasty bladder neck reconstruction in seven patients as a feasible and effective technique with all seven cases being considered a success at median follow up of eight months (55). RT was the stricture etiology in only three of seven patients, so larger studies are needed to evaluate the effectiveness of this robotic approach in the previously irradiated patient population.

Summary

The use of RT as a therapeutic agent in multiple pelvic malignancies is well supported in the oncologic literature. While technological advances in RT delivery have improved with a goal of minimizing unintended tissue injury, urinary retention and stricture after RT are not uncommon. Patients who develop AUR after RT should be managed with urgent bladder decompression. For those that develop obstructive symptoms or retention later after RT, transurethral intervention appears to be a reasonable initial option but is not without the potential for highly morbid complications. In those with advanced or refractory disease, open intervention through a multitude of approaches has been found to be safe and effective. While there is a paucity of literature surrounding the utilization of robotic reconstructive surgery in irradiated patients, initial reports seem to suggest it will be a useful tool to add to our surgical armamentarium.

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Footnote

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