

Urinary adverse effects of pelvic radiotherapy

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Objective: Radiation is an integral part of the treatment of many pelvic tumors. The cellular death induced by radiotherapy (RT) benefits cancer control but can also result in adverse effects (AEs) on the organ being treated or those adjacent to it. RT for cancers of the pelvis (bladder, prostate, rectum, uterus or cervix) can result in AEs in the urinary tract. While the acute urinary AEs of pelvic RT are well described, late AEs are less well characterized. The burden of treatment for late AEs may be large given the prevalence of tumors in the pelvis and the high utilization of RT to treat them.

Review: For prostate cancer, grade 1 and 2 urinary AEs following external beam radiation therapy (EBRT) are reported to occur in 20-43% and 7-19%, respectively, with a follow up of 10 years. Three-year cumulative risk for grade ≥ 2 urinary AEs is 28-30%. Following brachytherapy (BT), rates of urinary AEs at 5 years are reported to be 36%, 24%, 6.2% and 0.1% for Radiation Therapy Oncology Group (RTOG) grade 1, 2, 3, and 4, respectively. For bladder cancer, with a median follow-up of 5 years, 7-12% of patients who receive RT experience urinary AEs of grade 3 or more. For cervical cancer, there remains a 0.25% per year risk of severe AEs for at least 25 years following RT, and ureteral stricture is a well-described AE. For endometrial cancer, severe urinary AEs are rare, but at 13 years of follow up, patients report a significantly worse quality of life with respect to urinary function. In rectal cancer, preoperative RT has a lower risk of AEs than postoperative RT, and few urinary AEs are reported in the literature.

Conclusions: Urinary AEs can manifest long after RT, and there is a paucity of studies describing rates of these long-term AEs. It is important that the possible complications of RT are recognized by providers and properly communicated to patients so that they are able to make informed decisions about their cancer treatment.

Keywords: Pelvic radiotherapy; adverse effects (AEs); urinary tract; urinary toxicity

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Introduction

Cancers arising in the pelvis including the uterus, ovaries, cervix, rectum, urinary bladder and prostate account for 435,640 of the estimated number of new cancer cases in the United States in 2013. This represents 26% of all new cancers in 2013 in the United States (1). The development of radioactivity by Henri Becquerel in 1896 and the discovery of radium by Marie and Pierre Curie in 1898 led to a new period in medical technology (2). Pelvic radiotherapy (RT) now plays an important role in the management of these cancers. This treatment modality has been shown to have both early and late morbidity.

Pathophysiology of radiation-induced urinary tract injury

Radiation is an effective cancer treatment due to its direct and indirect interaction with living cells. The direct interaction induces immediate cell death by damaging DNA and/or tissue protein. The indirect interaction occurs by the formation of free radicals by ionizing radiation that interacts with enzymes leading to cell death and/or future mutation (3). These direct and indirect interactions lead to cellular injury by affecting division delay, reproductive failure and interphase arrest. All these consequences are more frequently encountered in rapidly dividing cells (4).

The radiation-induced damage to tissue architecture develops in a linear threshold model. Damage to the basement membranes of blood vessels can lead to occlusion, thrombosis and neovascularization. The atrophy and contraction of tissue results from increased proliferation of fibroblasts (5). All these changes have the potential to cause significant urinary tract injury. Bladder damage and loss of capacity can cause significant urinary symptoms. Neovascularization is an important factor for radiation cystitis and subsequent hemorrhagic cystitis. Replacement of the corpus spongiosum with fibrosis and subsequent occlusion of the urethral lumen is an important factor for the increased incidence of urethral strictures after RT (6).

Late urinary adverse effects (AEs) are usually graded using the Radiation Therapy Oncology Group (RTOG) system, which grades AEs on a scale of 0-5. Grade 0 denotes no complications. Minor AEs like microscopic hematuria are labeled grade 1. Grade 2 AEs include moderate urinary frequency, generalized telangiectasia, or intermittent macroscopic hematuria. Grade 1 and 2 AEs are commonly managed with observation or medical therapy and have minimal impact on quality of life. Grade 3 and 4 AEs are considered severe. These are often managed with a procedure and have a significant impact on quality of life. Grade 3 AEs include severe frequency or dysuria, severe generalized telangiectasia (often with petechiae), frequent hematuria, or a reduction in bladder capacity to less than 150 cc. Severe hemorrhagic cystitis, reduction in bladder capacity to less than 100 cc, and necrosis are classified as grade 4. Any death resulting from late complications of radiation is considered grade 5.

Prostate cancer

RT for patient controlled analgesia (PCa) is a well-established treatment modality whose importance has been increasing in recent years (7-9). During the past decade there has been a decrease in AEs of RT due to improvements in RT planning as well as the introduction of newer modalities that reduce both acute and late toxicity (10-13). Examples of these technological improvements include IMRT as well as real time tracking of the target while RT is delivered (14-16).

A direct comparison of the urinary AEs after different types of RT for PCa is difficult to perform due to differences in baseline clinical characteristics as well as heterogeneous reporting of end points (17). Nonetheless, patient factors have been shown to affect urinary morbidity

after RT for PCa. Specifically, worse comorbidities, pre-treatment urinary symptoms, larger prostate volume and prior TURP are well-established factors that affect the morbidity after RT (18-22).

External beam RT

The incidence of RTOG grade 1 and grade 2 urinary AEs after external beam radiation therapy (EBRT) is reported to be 20-43% and 7-19%, respectively, with a follow-up of up to 10 years (13,23-25). Mild symptoms can resolve either spontaneously or with treatment within 42 months after EBRT (24). Grade 3 urinary AEs occur at a rate of 5-13%. Radiation cystitis with gross macroscopic hematuria is the most common grade 3 AE of EBRT (25-27).

Peeters *et al.* randomized 669 patients to receive 68 and 78 Gy radiation doses by 3-D conformal radiotherapy (CRT) and compared early and late urinary AEs for both treatment arms. In their analysis there was no statistically significant difference between dose escalations with respect to urinary AEs ($P=0.3$). The 3-year cumulative risk for RTOG grade ≥ 2 urinary AEs was 28.5% for the 68 Gy arm and 30.2% for the 78 Gy arm. Nonetheless, patients experienced more early and late gastro-intestinal toxicity with higher radiation dose (27).

Harsolia *et al.* identified predictors for grade 2 and grade 3 chronic urinary toxicity secondary to 3-D CRT (28). In their prospective analysis they demonstrated that absolute bladder wall dose-volume endpoints and prostate volume $>150 \text{ cm}^3$ predict for the development of grade 2 and 3 late urinary AEs (all $P \leq 0.001$). Furthermore, grade 2 and grade 3 acute urinary AEs were strong predictors for the development of late AEs ($P \leq 0.03$).

Brachytherapy (BT)

Urinary AEs are one of the most significant side effects of BT for localized PCa and can follow a course from acute edema and radiation urethritis to chronic stricture. Evidence seems to suggest that acute symptoms improve with time in most men, once the initial edema has resolved. Early urinary retention (<12 months) has been reported in 7-25% of patients and irritative urinary symptoms were found in about 50% of patients (21,22,29). Urinary retention after a year post-implantation decreased significantly and has been reported by some to occur in as few as 1% of patients (22,30-32). Moreover, in an elaborate analysis of the literature relating functional outcomes and AEs of RT for

PCa, Budäus *et al.* reported that the predominant urinary toxicity following BT was related to radiation urethritis. They reported a peak increase in the International Prostate Symptom Score (IPSS) of 7-12 units above the baseline at 2-10 weeks post implantation. Symptoms then resolved in more than 75% of cases at one year (17).

Martens *et al.* retrospectively reviewed predictors of urinary retention in 207 BT patients. In their model, pre-implant peak flow rate and prostate volume were statistically significant predictors of post-implant urinary retention. They estimated that for every one-unit increase in peak flow rate the odds of catheterization decreased by 6% (33).

When analyzing predictors of acute toxicity (<6 months), Keyes *et al.* determined that a greater baseline IPSS ($P<0.001$), larger degree of post-implant edema ($P<0.001$) and a larger pre-implant prostate volume ($P=0.02$) increased the likelihood of acute RTOG grade 3 urinary AEs. When focusing on late grade ≥ 2 urinary AEs, predictors included greater baseline IPSS, maximal post-implant IPSS, presence of acute toxicity and higher prostate V150 (volume of the prostate covered by 150% of the dose) (all $P<0.05$) (34).

The rate of urinary AEs at five years is reported to be 36%, 24%, 6.2% and 0.1% for RTOG grade 1, 2, 3, and 4 respectively (34). Late grade 2 urinary AEs affects 19-41% of patients following BT. Symptoms include hematuria, and obstructive and irritative symptoms (35-37). Urethral strictures (grade 3) following BT occur in 1-12% of cases with an increased risk if combination therapy with EBRT is used (37,38).

There is a debate in the literature as to the optimal management of urinary retention following BT. Kollmeier *et al.* reviewed their population of patients undergoing TURP after BT for urinary retention. The rate of incontinence was 18%, ranging from minimal leakage to requiring greater than five pads daily (39). Conversely, Mabweesh *et al.* analyzed a small subgroup of patients who underwent TURP for urinary retention following BT and found no cases of incontinence following this procedure (40).

In addition to detailing the rate of AEs, it is important to understand how these impact the patients' quality of life (41-46). Sanda *et al.* prospectively identified the determinants of health-related quality of life after primary treatment of PCa (42). Urinary AEs after BT were associated with urinary irritation/obstruction, and urinary incontinence (all $P<0.001$). The rate of urinary incontinence after BT was reported to be 4% and 6% of patients at one and two years after treatment, respectively. Eighteen percent of patients in the BT group and 11% of those in the external beam RT

group reported having moderate or severe distress from overall urinary symptoms at 1 year. Large prostate size and hormonal treatment exacerbated urinary irritation after BT or RT (all $P<0.03$). Limitations of the study included its lack of randomization to treatment as well as its short follow-up of 2 years.

Compromised wound healing, distorted tissue planes and altered blood supply in irradiated prostate cancer patients can contribute to urethroplasty failure (47). Factors that contribute to urethroplasty failure include: complex nature of the stricture, difficult location and pronounced tissue damage secondary to radiation (48). The average stricture length after EBRT is estimated at 2 cm. Compared to BT, EBRT strictures are not commonly obliterative and can be less complicated to treat. Although anastomotic repair can be acceptable for very short strictures, most authors tend to suggest a patch repair with a flap as this is safer. Conversely, after both EBRT and BT, the average stricture length is longer (4 cm) and nearly half are obliterative. Recovery is slow and recurrence is significant (6).

Glass *et al.* retrospectively reviewed urethral stricture formation following RT for prostate cancer. In their cohort of 29 men, 76% underwent excision and primary anastomosis, while 17% underwent substitution urethroplasty. Although reporting an overall success rate of 90%, complications were not uncommon and at times required further surgical treatment (47). Incontinence after urethroplasty for radiation-induced stricture disease is reported to be as high as 50% (49).

Bladder cancer

Bladder conservation techniques using a combination of trans-urethral resection of bladder tumor (TURBT), chemotherapy and RT have yielded favorable results (50-52). Several prospective studies have shown a 5-year overall survival ranging from 50-60% (53-55). Thus trimodal therapy or bladder conservation protocols are now a treatment option for selected patients with muscle invasive bladder cancer (56-58). Radiation is rarely used in combination with radical cystectomy so most of the radiation-induced urinary AEs with respect to bladder cancer come from the bladder conservation literature using trimodal therapy.

Common acute radiation-induced AEs include transient cystitis and enteritis. The acute symptoms have been reported to resolve within two weeks after completion of chemo-RT (59). However, Fokdal *et al.* in their tolerability study using a modified protocol of trimodal therapy

employing weekly cisplatin doses, reported that 45% of patients registered changes in their bladder habits. Furthermore, 14% reported a moderate to severe impact of the treatment on their function with a follow-up of 29 months (60). Urinary AEs were also reported by James *et al.* in their multicenter phase 3 trial comparing RT with or without synchronous chemotherapy. At 1 year they reported grade 3 or 4 urinary AEs in 1-3% of patients. There was no statistically significant reduction in bladder volume at 1 and 2 years from baseline (61). Other studies have reported that with a median follow-up of 5 years, 7-12% of patients experienced late urinary AEs as defined as RTOG grade 3 or more (62,63). Bladder toxicity more than RTOG grade 3 is very rare (54,64).

Rödel *et al.* reported their 18-year experience with bladder preservation protocols. Acute radiation-induced bladder toxicity was infrequent (2%) and easily managed by symptomatic treatment. At a median follow-up of 5 years, 10% of patients reported increased urinary frequency with nocturia, 3% of patients had a reduced bladder volume with less than 2-hour intervals of micturition. Two percent of their population underwent salvage cystectomy due to a contracted bladder (54). In a retrospective analysis of radical RT administered between 1975 and 1995, Majewski *et al.* demonstrated that T-stage ($P=0.004$) was the only statistically significant factor affecting bladder toxicity after RT (63).

In a retrospective review of long-term survivors in patients who underwent trimodal therapy, Zietman *et al.* reported urodynamic and quality of life data (65). Twenty-one percent of patients reported bladder hypersensitivity, involuntary detrusor contractions and incontinence. Of all women, 11% wore pads. Distress from urinary symptoms was half as common as prevalence. Despite higher rates of urinary symptoms, global health-related quality of life was high (65). In an older series with longer follow-up of patients who had radical RT for bladder cancer, 74% of patients reported little or no distress from symptoms related to their urinary tract (66).

Rectal cancer

An estimated 40,340 rectal cancers occurred in 2013, and 90% of cases are diagnosed in people over the age of 50 (1). Total mesorectal excision (TME), which consists of the removal of all mesorectal fat and lymph nodes, is the surgical standard of care in rectal cancer; still, 52% of patients undergo RT within six months of diagnosis (67,68). At more advanced stages of disease, many studies have demonstrated decreased

local recurrence with adjuvant chemoradiotherapy when compared with surgery alone. Preoperative RT has been found to have fewer severe AEs of any system when compared with postoperative RT (27% *vs.* 40% acute and 14% *vs.* 24% late) and one study even found improved overall survival with preoperative treatment. Postoperative complications like anastomotic leakage, delayed wound healing, bleeding, and ileus were not significantly different between the two groups. Therefore, a preoperative course of neoadjuvant RT is recommended for rectal cancers that are T3 or have regional lymph node involvement (stage II or III) (69-71). RT is typically administered as CRT in 2 Gy fractions up to a total dose of 46-50 Gy over 20+ weeks, or in 5 Gy fractions up to 25 Gy over five days (67,69).

We expect to see urinary AEs following RT for rectal cancer due to the close proximity of the rectum to the bladder, as well as its blood and nerve supply. One trial reported urinary AEs such as frequency, cystitis, incontinence, urinary retention, and ureteral stricture. Severe late urinary AEs were rare (4%) but AEs were potentially severe, with one patient requiring daily catheterization for grade 3 urinary retention, one requiring nephroureterectomy for a grade 4 stricture, and two requiring urinary diversion for grade 4 incontinence (72). Another trial with a median follow-up of 85 months demonstrated incontinence at least twice weekly in 25% of patients (73). Surgery itself may play an important role in the development of urinary dysfunction due to autonomic nerve damage, still one study with a mean follow up of 15 years found that although urinary incontinence was common in both irradiated and non-irradiated patients, it was significantly more so in those who received RT (45% *vs.* 27%, $P=0.023$) (74). Additionally, a retrospective study of 535 patients compared TME + RT *vs.* TME only, and found all grades of urinary incontinence to be more common in the TME+RT group (36% *vs.* 24%, $P=0.007$) (75). Though most studies do not track urinary AEs in the setting of RT for rectal cancer, the studies do demonstrate that RT has a significant impact on urinary function with potentially severe AEs, although these are rare.

Cervical cancer

An estimated 12,340 new cases of invasive cervical cancer were diagnosed in 2013 in the United States. While incidence rates of invasive cervical cancer in women aged 50 and older have been declining in recent years, rates have remained stable in women under 50, the latter group making up 59% of new diagnoses (1). While RT and radical

surgery are equivalent in stage IB to IIA disease, RT is integral to the treatment regimen for stages IIB and greater. Adjuvant RT in addition to surgery may also be indicated for patients with particular risk factors (e.g., high grade tumor, lymphovascular space involvement, positive margins, multiple positive nodes). Optimal RT consists of EBRT and intracavitary high dose rate-BT for a combined dose of 80-90 Gy (76). Overall, 53% of women receive RT within six months of diagnosis (68).

Sixty percent of urinary AEs due to RT develop more than two years following treatment, in contrast to bowel AEs, of which 80% develop within the first two years (77,78). Annual incidence rates for urinary AEs actually increase between years three and five post-RT, from 18% to 28%, respectively (77). Minor (grade 1 or 2) AEs are more common than major AEs; 44% develop acute (<90 days after RT) minor urinary AEs, and 7-9.5% develop late minor AEs (79-81).

The posterior bladder and insertion point of the ureters lie directly anterior to the cervix, making these areas most susceptible to injury. The most common major urinary AEs (grade 3 or above) are ureteral stenosis, vesicovaginal fistula, and hematuria (79). The risk of developing major urinary AEs is greatest in the first three years following treatment (0.7% per year) but there remains a constant actuarial risk of 0.25% per year for at least 25 years (79,82). In studies with more than three years of follow-up, risk of developing a major urinary AE ranges from 1.3-14.5% (80,83-85). The delay between RT and AEs can be substantial; ureteral stricture has been observed 29 years after RT for cervical cancer, and spontaneous bladder rupture has been reported as late as 30 years after (86,87). Risk of increasingly severe AEs following RT is significantly associated with larger doses of radiation and number of treatments (79,80,86). Though RT-induced urinary AEs can be seen long after treatment, a systematic review found that 14 of 17 trials of RT plus chemotherapy did not routinely record late AEs (88).

Post-RT ureteral strictures are difficult to manage, in contrast to the ureter injured during gynecologic surgery, which can be reimplanted into the bladder with success rates over 90% (89,90). The stenotic ureter after RT is typically managed with repeated stenting; reimplantation is often not possible due to an ischemic distal segment. Stents must be exchanged every three months under anesthesia and may cause infections, bladder pain, urinary frequency and urgency. When prolonged stenting is not tolerated, urinary diversion or nephrectomy may be required (91-93).

Endometrial cancer

An estimated 49,560 cases of uterine cancer occurred in 2013, most of which were in the endometrium (1). More than 90% of cases occur in women over the age of 50, with a median age of 63 (94). The initial approach to endometrial cancer is total hysterectomy and salpingo-oophorectomy; but in 2006, 23% of patients with endometrial cancer also underwent RT within six months of diagnosis (68). The PORTEC-1, GOG99, and ASTEC-EN.5 trials demonstrated that RT following surgery for stage I disease reduces locoregional recurrence but does not improve overall or disease-specific survival, and is associated with increased AEs (95-98). Therefore, RT is indicated as adjuvant therapy in patients with features of high-intermediate risk (about 30% of endometrial cancers) or as salvage therapy in patients with recurrent disease (97,99) where there is a survival benefit to balance the increased risk of toxicity. RT is administered as either EBRT or vaginal BT for a total of 45-50 Gy to the target tissue. The PORTEC-2 trial demonstrated that BT is equally effective when compared to EBRT in preventing locoregional recurrence and improving survival, with fewer AEs (99).

The uterus resides within the peritoneum directly posterior to the bladder; thus, most AEs following RT involve the bladder and bowel. Contrary to RT for cervical cancer, ureteral stricture is rare and urinary AEs in general are much less common. Only one small series reported a 6% rate of grade 4 ureteral stricture with hydronephrosis after HDR-BT (100). The PORTEC-1 and 2 trials, with median follow-ups of 52 and 45 months, respectively, demonstrated no severe urinary AEs (96,99). Late AEs of any grade occurred in 25% of patients who underwent RT *vs.* 6% in patients who only received surgery ($P<0.0001$). GI AEs were most common, 68% of which were grade 1. Severe GI AEs occurred in about 2% of patients (96,99). Urinary AEs include minor incontinence, urinary frequency, or brief episodes of cystitis (96). The GOG99 trial, with a median follow up of 68 months, found minor urinary AEs in 30% of the RT group and in 8% of the non-RT group ($P<0.001$) (97). The patient-reported quality of life at a median follow up of 13 years in the PORTEC-1 trial cohort who underwent EBRT indicated a significantly worse quality of life with respect to urinary urgency, needing to remain close to a toilet, incontinence, and limitation of daily activities (101).

Conclusions

Radiation-induced injury of the urinary tract is a complex

and debilitating complication and can lead to significant morbidity for the patient. There is a paucity of trials powered to reliably measure the rate of high-grade AEs after RT. Studies are limited by small sample size and short follow-up; this can underestimate RT morbidity, since this condition is relatively infrequent and its effects occur over a long time horizon. An improved understanding of RT AEs in general and late AEs in particular should aid patient-provider discussions of the risks and benefits of their treatment options and highlight areas for future research into ways to minimize these unintended consequences of care.

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Footnote

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