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Long-term urinary adverse effects of pelvic radiotherapy

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Abstract

Objective—Radiation for tumors arising in the pelvis has been utilized for over a 100 years. Adverse effects (AEs) of radiotherapy (RT) continue to accumulate with time and are reported to show decades after treatment. The benefit of RT for pelvic tumors is well described as is their acute AEs. Late AEs are less well described. The burden of treatment for the late AEs is large given the high utilization of RT.

Review—For prostate cancer, 37% of patients will receive radiation during the first 6 months after diagnosis. Low- and high-grade AEs are reported to occur in 20–43 and 5–13%, respectively, with a median follow-up of ~60 months. For bladder cancer, the grade 2 and grade 3 late AEs occur in 18–27 and 6–17% with a median follow-up of 29–76 months. For cervical cancer, the risk of low-grade AEs following radiation can be as high as 28%. High-grade AEs occur in about 8% at 3 years and 14.4% at 20 years or ~0.34% per year. Radiation AEs appear to be less common or at least less well studied after radiation for rectal and endometrial cancers.

Conclusion—Properly delineating the rate of long-term AEs after pelvic RT is instrumental to counseling patients about their options for cancer treatment. Further studies are needed that are powered to specifically evaluate long-term AEs.

Keywords

Radiotherapy; Pelvic cancers; Prostate cancer; Bladder cancer; Cervical cancer; Endometrial cancer; Rectal cancer; Radiation adverse effects; Hemorrhagic cystitis; Urethral strictures; Ureteral strictures

Introduction

Cancers arising in the pelvis account for up to 18% of all cancers [1]. Radiation therapy (RT) has been utilized in treatment of these cancers for more than 100 years, with its earliest roots traced to the discovery of X-rays in 1895 by Wilhelm Röntgen. Due to their anatomical location, the lower ureters, bladder and posterior urethra are exposed to radiation during treatment for pelvic cancers, giving rise to a variety of urinary adverse effects (AEs). Although serious complications occurred with early forms of RT, technological advancement in the delivery of RT has significantly reduced the AEs. Short-term AEs of RT are well described and generally well tolerated. Although the long-term urinary AEs of pelvic RT can be severe, they are thought to be rare; but long-term data are lacking. With about 360,000 Americans diagnosed with cancers of the prostate, bladder, cervix, uterus or

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rectum each year [1] and ~50% receiving RT, the burden of urinary RT AEs is significant [2] and will continue to be more important as long-term survivorship is improved.

Radiation therapy adverse effects

Radiation causes its therapeutic effect by damaging DNA content of actively dividing cells. AEs are usually secondary to chronic fibrosis and progressive endarteritis in poorly oxygenated submucosal and muscular tissues, with eventual tissue scarring. This is expressed by radiation cystitis, defunctionalized bladder due to scarring, hemorrhagic cystitis due to breakdown of mucosa secondary to loss of supporting submucosal blood supply, ureteral and urethral strictures, as well as fistulas [3,4]. Acute AEs occur within 90 days of treatment. The short-term incidence of radiation AEs occurring within the first 5 years is well documented, but not long-term effects. Long-term follow-up of surgically treated patients shows that the morbidity of surgery is primarily suffered in the first year [5]. In contrast, post-radiation urinary AEs continue to accrue decades after RT [6,7]. As cancer control rates improve, long-term survivorship issues become highly relevant to cancer management. A better understanding of the long-term risk of urinary AEs of pelvic RT is thus integral to treatment decision-making at the time of cancer diagnosis and to survivorship care of RT-treated patients.

The two most common forms of RT are brachytherapy (BT) and external beam RT (EBRT). Because toxicity to surrounding organs limits the RT dose, advances in RT delivery such as multimodality therapy (BT+EBRT), three-dimensional conformal RT (3D-CRT) and intensity modulated RT (IMRT) have been designed to focus the radiation on the target organ, allowing dose escalation to the tumor site, while minimizing adjacent organ damage. The combination of therapeutic effect and decreased side effects has led to an increase in utilization as evidenced by a review of the Surveillance Epidemiology and End Results (SEER) database [2] (Fig. 1).

The National Cancer Institute defines a grading system for the identification and classification of AEs of cancer therapy: the Common Terminology Criteria for Adverse Events (CTCAE) [8]. Its use is required in clinical trials of cancer therapeutics. AEs due to any cancer therapy (chemotherapy, surgery or RT) are graded from 1 to 5, depending on severity (Table 1). A similar grading system has been used by the Radiation Therapy Oncology Group (RTOG) for clinical documentation of AEs outside of the trial setting [9,10].

Radiation therapy and prostate cancer

In 2009, prostate cancer affected an estimated 192,280 men with a median age at diagnosis of 68 years [1]. It represents 71% of all pelvic tumors in men. According to a review of the SEER database, 37% of prostate cancer patients are treated with RT within 6 months of diagnosis [2], with 26% receiving EBRT and 15% BT. The treatments are delivered alone or in combination. Historically, the dose delivered to the prostate by conventional EBRT was 60–68 Gy with the dose-limiting factor being toxicity to adjacent organs, namely the bladder and the rectum. Through increased target specificity, 3D-CRT and IMRT may now allow safe delivery of radiation doses to the prostate in the range of 78–84 Gy [9–11]. Permanent seed implants (LDR-BT) typically deliver 125–145 Gy to the prostate.

The benefits of RT for prostate cancer are well documented in literature. Thompson et al. showed that men randomized to receive adjuvant EBRT for locally advanced prostate cancer after prostatectomy experienced improved metastasis-free survival as well as overall survival [12]. Cohort series suggest 10-year cancer control outcomes for low- and intermediate-risk prostate cancer are similar regardless of whether men are treated with

surgery, EBRT or BT [13–15]. For this reason, the AEs of therapy are an important consideration in selecting primary therapy for prostate cancer.

Urinary AEs following EBRT for prostate cancer are varied. In general, the incidence of persistent grade 1 symptoms (>90 days after RT) is reported to be 20–43% with a follow-up of up to 10 years [16–19]. The incidence of late grade 2 AEs is reported to be 7–19% [16–18]. However, these symptoms continue to accrue with time: the actuarial risk of genitourinary AEs of grade 2 or greater was 15% following 3D-CRT at 3 years and 19% by 5 years [18]. Of those who develop mild to moderate AEs, many appear to resolve, either spontaneously or with treatment. In a study by Zelefsky et al. 64% of patients with late grade 2 urinary toxicity following 3D-CRT had subsequent resolution or significant improvement of their symptoms within 42 months [17].

Grade 3 urinary AEs occur in 5–13% after EBRT [19,20]. Like grade 2 AEs, grade 3 AEs continue to accrue with long follow-up. Indeed, in one EBRT trial, grade 3 urinary AEs occurred in 5–7% at 31 months and 12–13% at 51 months [19–21]. Hemorrhagic cystitis is the most common grade 3 complication of prostate RT. Grade 3 and 4 hematuria was reported in 8.7% of patients with onset up to 10 years following RT [22]. Advances in EBRT technology are intended to increase the specificity of radiation and minimize adjacent organ damage. However, radiation oncologists have used this as an opportunity to increase the delivered dose, resulting in better tumoricidal activity but also increased damage to the target organ. Although dose escalation with IMRT lowered rectal toxicity, it actually increased the urinary toxicity [11]. The urethra may not be spared any better with IMRT than with conventional EBRT.

Late grade 2 AEs following BT affect 19–41% of the patients and most commonly include hematuria and obstructive or irritative urinary symptoms [23–25]. Urethral strictures (grade 3) following BT occur in 1–12% of men; risk is increased by combination therapy with EBRT and is related to the dose delivered to the apex of the prostate [25,26]. With short follow-up, grade 4 urinary AEs (life-threatening hematuria or necrotic/contracted bladder) appear to be rare (<1%) after BT or EBRT [11,26,27]; however, with extended follow-up, the rate increases to 2% after EBRT or 3.3% after BT+EBRT [19,27]. A SEER-Medicare examination showed that within 2 years of BT, 10% had a procedure performed for a urinary AE [25]. Risk factors included older age, non-white race, low income, co-morbidities, combination therapy with EBRT or hormonal therapy and history of prior transurethral resection of the prostate.

Radiation therapy and bladder cancer

In 2009, the incidence of bladder cancer was expected to approach 71,000 among US men and women [1]. Median age at diagnosis is 73 years. Approximately half are diagnosed with invasive tumors. Radical cystectomy is the most common treatment in muscle invasive bladder cancer; 8% receive EBRT and BT is rare [2]. However, recent success rates with EBRT (45–65 Gy of 3D-CRT) plus adjuvant chemotherapy approach those with surgery: 34–48% remain cancer-free with an intact bladder at 5 years [28–30]. Current guidelines support chemotherapy and EBRT as an option in invasive bladder cancer [31].

Late grade 2 AEs with EBRT for bladder cancer have been reported to occur in 18–27% [32]. In a study by Fokdal et al. 261 patients received 60 Gy of EBRT. With a median follow-up time of 29 months (range 18–103), 45% registered changes in their bladder habits and 14% reported moderate to severe impact of the treatment on their bladder function [33].

The cumulative incidence of grade 3 or higher urinary AEs after bladder RT is 6–17% with follow-up ranging from 29 to 76 months [29,33–35]. Urinary blood clots can occur in 18%,

incontinence in 20% and urinary frequency more than once an hour in 50% at 3 years [36]. Two series report the incidence of grade 3–4 AEs collectively as 14.5 and 25%; when separately recorded, grade 4 AEs occur in 0–3% [29,32,37,38]. Studies with the largest patient population and the longest follow-up [35,39] note the highest rate of AEs. BT is rare in bladder cancer but HDR-BT is associated with high AE rates (17% Grade 4) [40].

Radiation therapy and colorectal cancer

An estimated 41,000 Americans were diagnosed with adenocarcinoma of the rectum in 2009, at a median age of 71 years [1]. The most common treatment is surgical resection; still, 52% receive RT within 6 months of diagnosis [2]. RT is universally given as preoperative EBRT, generally at doses of 40–50 Gy. Indications for EBRT include T3 disease or local adenopathy [41]. Preoperative EBRT in such patients improves survival [42,43]. In a Swedish study evaluating 1,168 patients randomized to surgical treatment with or without preoperative EBRT (25 Gy), overall survival (58% vs. 48%) and recurrence-free survival (27% vs. 11%) both improved at 5 years with EBRT [43]. Immediate postoperative complications (anastomotic leak, wound infections, death) were not significantly higher in the neoadjuvant RT group [44]. Dose escalation resulted in better tumor response [42].

Urinary AEs have not been properly evaluated in the setting of RT for colorectal cancer. The only trial that describes urinary AEs mentions “bladder problems” in 2–4% [44]. Given the close proximity of the bladder as well as its blood and nerve supply to rectum, there is likely to be an additive effect of RT and surgery causing increased risk of bladder dysfunction, although the lower doses of RT used for colorectal cancer may mitigate this effect.

Radiation therapy and cervical cancer

About 11,270 US women were estimated to be newly diagnosed with cervical cancer in 2009. Cervical cancer tends to be a disease of younger women, with a median age of 48 years [1]. Radical hysterectomy and primary radical RT are equivalent in Stage IB to IIA disease, and RT is integral to the treatment of more advanced disease ($\geq$ IIB) [37,38]. Radical RT is delivered as 40–50 Gy EBRT plus 20–40 Gy HDR-BT for total doses to the cervix of up to 90 Gy. Overall, 53% of women receive RT within 6 months of diagnosis [2].

Eifel et al. reported that minor grade 1 or 2 urinary tract complications occurred most often during the first 3 years after treatment [45]. The risk of developing grade 1 and 2 AEs following RT for cervical cancer has been reported to be 28% [48] and increases by an additional 17.4% at 5 years [45].

Patients who survived 3 years after treatment had a 7.7% probability of a major (grade 3) complication from RT. At 5 years, the risk of a major complication was 9.3% and there was a subsequent continuous risk of ~0.34% per year, resulting in an actuarial risk of major complications of 11.1% at 10 years, 13% at 15 years and 14.4% at 20 years [45–47]. Grade 3–4 urinary AEs occur in 1.3–14.5% in series with at least 3 years of follow-up [46–49]. Case reports demonstrate that spontaneous bladder rupture can occur as much as 30 years after RT for cervical cancer [5,51]. Ureteral stricture and radiation cystitis are the most common urinary complications. The ureters insert into the posterior wall of the bladder just anterior to the cervix. A systematic review found that 14 of 17 trials of RT plus systemic chemotherapy did not routinely record late AEs [50].

Radiation therapy and endometrial cancer

The 2009 estimate for new diagnosis of uterine cancer in US women is 42,160; nearly, all of these will be endometrial carcinomas [1]. The mean age at diagnosis is 62 years and extrafascial hysterectomy is first-line treatment for localized disease [2].

HDR-BT and/or 3D-CRT have an important role in adjuvant therapy for high-risk disease or salvage therapy for a local recurrence after hysterectomy [52]. In 2006, 23% of new diagnoses underwent RT within 6 months of diagnosis [2], with many more likely receiving salvage RT at a later date; 14.9% received external beam radiation therapy and 12.6% received BT. RT rates may be expected to rise in response to data from two recent trials (Gynecologic Oncology Group-99 or GOG99 and Postoperative Radiotherapy for Endometrial Cancer or PORTEC) showing improved survival with whole pelvis adjuvant RT (46–50 Gy) compared to observation in women with high-risk cancer features at hysterectomy [53,54].

Low-grade AE with radiation for endometrial cancer was reported in 11–16% of the patients [53–55]. The majority of those tend to be grade 1. With median follow-up of 52 and 68 months, the PORTEC and GOG99 trials noted no grade 3–4 urinary AEs [53,54]. Likewise, many other cohort series report severe urinary AEs to be nonexistent or rare with pelvic EBRT or BT for endometrial cancer [55,56]. However, the longest median follow-up in any of these series is only 5.5 years. Indeed, only one case series reports any significant rate of severe urinary AEs: a 6% incidence of ureteral stricture after HDR-BT [57]. The lower rate of urinary AEs after uterine RT compared to cervical RT may be due to differences in follow-up, in anatomic position relative to the ureters or the lower doses of EBRT delivered as adjuvant therapy after hysterectomy rather than high doses of BT+EBRT used as sole therapy in cervical cancer.

Discussion and conclusions

Overall, these data suggest that the majority of urinary AEs after pelvic RT are grade 1–2 with grade 3 or more AEs being less common. However, all urinary AEs continue to accrue with time. Severe late urinary AEs are most common after prostate, bladder and cervical RT. This may relate to the higher doses of RT used and/or the anatomic proximity of these tumors to the urinary system compared to the uterus and rectum. Furthermore, BT+EBRT is common in prostate and cervical cancer and combination therapy is a risk factor for AEs. Lastly, it is possible that late urinary AEs are recognized more often after bladder and prostate RT due to detection bias as these patients are regularly seen by urologists. We also note that the type of AE varies by tumor type: urethral stricture occurs primarily after prostate BT, bladder hemorrhage and necrosis are sequelae of bladder RT and ureteral strictures are most common after cervical RT. Still, several factors limit our understanding of the incidence of and risk factors for urinary AEs after RT.

There is a paucity of trials powered to reliably measure the rate of high-grade AEs. The primary intent of most of the pelvic RT series in the literature is to study cancer control rates. As such, many do not specifically document urinary AEs; most are underpowered or are of insufficient follow-up to measure severe late urinary AEs. Comparing the incidence of urinary AEs across studies is made difficult by the variability in study design and follow-up. Different dosages of RT or combinations of therapy are given and no standard method is used to detect AEs. Also, the majority of trials report the crude rate rather than the actuarial incidence leading to an underestimate of the rate of severe urinary AEs with long-term follow-up. The few trials with longer follow-up and appropriate censoring of patients suggest urinary AEs continue to accrue at a steady rate even two decades after RT. The true

incidence of severe urinary RT AEs among long-term cancer survivors may be as high as 20%.

AEs after surgery tend to occur immediately but radiation effects accumulate over the long-term and their true burden may be underestimated. In conditions where surgery and radiation are alternative treatments, such as in prostate or bladder cancer, this may alter the discussion of the relative risks and benefits of surgery versus radiation. Thus, a proper understanding of the rates and severity of AEs is important to improving shared decision making about pelvic cancer treatments. Efforts should be made to better understand the burden of and treatment for urinary AEs of pelvic radiation.

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Fig. 1.
Rates of RT (EBRT or BT) within 6 months of diagnosis of pelvic malignancy. Note the significant rise in RT rates among prostate and rectal cancer patients. Raw data compiled by authors from SEER public use file

Table 1

CTCAE version 4.0: a systematic grading system for AEs of cancer therapy and late AE as per RTOG

Grade	CTCAE	RTOG—Acute	RTOG—Chronic
0	No change	No change	No change
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated		Slight epithelial atrophy, mild telangiectasia (microscopic hematuria)
2	Moderate, local or noninvasive intervention indicated; limiting instrumental activities of daily living (ADL)	Frequency of urination or nocturia less frequent than every hour, dysuria, urgency bladder spasm requiring local anesthetic (for example phenazopyridine hydrochloride)	Moderate frequency, generalized telangiectasia, intermittent macroscopic hematuria
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Frequency with urgency and nocturia hourly or more frequently, dysuria, pelvic pain or bladder spasm requiring regular, frequent narcotic, gross hematuria with or without clot passage	Severe frequency and dysuria, severe generalized telangiectasia (often with petechiae). Frequent hematuria, reduction in bladder capacity (<150 cc)
4	Life-threatening consequences; urgent intervention indicated	Hematuria requiring transfusion, acute bladder obstruction not secondary to clot passage, ulceration or necrosis	Necrosis, contracted bladder capacity (<1,000 cc), severe hemorrhagic cystitis
5	Death	Death	