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RECONSTRUCTED BLADDER FUNCTION & DYSFUNCTION (M KAUFMAN, SECTION EDITOR)

Consequences of Pelvic Radiotherapy on Urinary Function in Women

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Abstract

Purpose of Review The objective of this review is to critically evaluate recent literature on the urinary complications following pelvic radiation for malignancy in women.

Recent Findings Lower urinary tract symptoms (LUTS) manifest in a significant population of women post-radiation with confirmed objective findings on urodynamic evaluation. Other serious consequences such as fistula, hemorrhagic cystitis, and strictures are less common but can be significant.

Summary The sequelae of radiation on the female lower urinary tract can range from mild symptoms to those requiring major surgical intervention. Therefore, post-radiotherapy patients must be approached with vigilance in conjunction with thorough preoperative counseling.

Keywords Radiation cystitis · Ureteral obstruction · Vesicovaginal fistula · Rectovaginal fistula · Radiation injury

Abbreviations

EBRT	External beam radiation therapy
IBRT	Internal beam radiation therapy
ROS	Reactive oxidative species
SASP	Secretory profile of senescence
HDR	High dose rate
LDR	Low dose rate

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Introduction

Radiation, specifically X-rays, was discovered in 1895 by Wilhelm Conrad Roentgen and was first used for therapy a year later by Emil Herman Grubbe for treatment of breast cancer patients [1]. Other scientists such as Antoine Henri Becquerel, Marie Sklodowska-Curie, and Pierre Curie contributed to the evolving field by discovering natural sources of radiation which were important to harnessing the therapeutic effects of radiation. By the 1920s, delivery technique and dosing had improved along with the understanding of the complications from radiotherapy. Ideas such as using fractionated instead of singular treatment sessions demonstrated improved oncological outcomes with less side effects. There have been vast improvements in technology to deliver more precise doses of radiation such as brachytherapy, proton beam therapy, 3D conformal radiotherapeutic device (stereotactic radiation therapy), and image-guided radiotherapy. However, adverse effects of therapy remain a devastating reality for patients. The purpose of this paper is to provide an updated overview of the post-radiation urinary complications in female patients.

Mechanism of Action

Radiation provides therapeutic effect by inducing cellular damage in a multifactorial pathway, including the (a) creation

of reactive oxidative species (ROS), (b) modification of enzymatic functions of specific proteins, (c) induction of senescence in normal stem cells, and (d) activation of immune modulators. All of these modalities work in conjunction to create acute and late-stage injuries to both malignant and collateral damage to non-malignant tissue. In addition to the intended effect, radiation impact to the non-malignant tissues can have adverse consequences [2].

A) Reactive oxygen species (ROS)

Application of an ionizing radiation beam to cellular tissue not only directly leads to DNA/RNA breakage but it also induces hydrolysis of water molecules, resulting in the creation of free radicals, or reactive oxygen species (ROS). These ROS inflict secondary damage to the DNA, RNA, proteins, and cell membranes. ROS effects are exponentially propagated when activating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway in the neighboring endothelial, epithelial, and inflammatory cells. This in turn upregulates over 200 genes, including NADPH oxidase, to create highly toxic metabolites called superoxide (SO) and nitric oxide. SO is especially destructive as it can self-propagate to produce more free radicals in the system. Another effect of the activation of Nrf2 is increase modification of proteins by isoleuvoglandin (IsoLG) which can lead to late tissue injury [2].

B) Metabolic changes

Another major component of radiation-induced tissue damage is changes to cellular metabolism. Diseased tissue, in its hypoxic and inflamed state, demonstrates increased activation of the transcription factor hypoxia-inducible factor 1 α (Hif-α). This secondarily enhances transforming growth factor-β_1 (TGF-β_1) and vascular endothelial growth factor (VEGF) to promote cell proliferation, immune suppression, and inflammation—all of which propagate late-stage radiation injuries.

Lack of cellular metabolism can exacerbate the oxidative stress pathway as demonstrated by the decrease levels of tetrahydrobiopterin (BH4), a metabolite which normally binds to endothelial nitric oxide synthase. Its deficiency can lead to increased levels of SO and peroxynitrite. These metabolic changes enhance the long-term tissue damage linked to toxic metabolites [2].

C) Senescence

Senescence is the arrest of further cell growth or division, which normally occurs when telomeres reach their limiting length, resulting in the natural aging process. Radiation-induced senescence is also an arrest, but of normal stem cell tissues which become unable to replace damaged parenchymal cells. These senescent cells secrete proinflammatory molecules called secretory profile of senescence (SASP) such as IL, IL-6, TGF-β, TNF-α, VEGF, and EGF which exacerbate tissue damage [2].

D) Activation of immune actors

Late damage from radiation is also mediated by immune cells such as macrophages and T cells. Upon radiation exposure, cytokines such as IL-13 are released, inducing macrophages to their phenotypic M_2 phase. These macrophages then release TGF-β which further worsens tissue fibrosis [2].

Similarly, CD4+ T cells have been implicated in a minor role, creating late-stage radiation injuries. Though the mechanism is still being investigated, there have been studies demonstrating a correlation between higher concentration of CD4+ T helper cells and GU toxicities such as diarrhea and radiation cystitis [3].

Delivery Modalities

Radiation can be categorized as non-ionizing (i.e., radio waves, microwaves, visible light) or ionizing (i.e., photon beam, X-rays, proton, electron, neutron, carbon ions, alpha, and beta particles), with the latter type employed in cancer treatment. Delivery can be two-fold: external beam radiation therapy (EBRT) or internal beam radiation therapy (IBRT) (i.e., brachytherapy), both of which are integral to the treatment of pelvic malignancies [4].

EBRT is defined as having an outside radiation source which produces radioactive beams directed towards a targeted internal organ. As such, there is an "entry" and "exit" point of the body with calculated doses of radiation to the tissues in the trajectory. Improvements to decrease radiation exposure to healthy organs include technology such as image modulated radiotherapy (IMRT) which utilizes multileaf collimators (MLC) which are directed to move and block excessive radiation to non-targeted organs. Another option to reduce the dosage to normal tissue is volume-modulated arch therapy (VMAT), which allows continuous rotation around the patient during treatment so that no beam trajectory bears the full amount of radiation. Proton therapy also reduces the radiation load as the beam stops at the targeted organ, avoiding injury to the normal tissue posterior.

On the other hand, IBRT, or brachytherapy, is categorized as having an internal source of radiation, which is often conducive to the treatment of pelvic malignancies due to available access. This typically involves implantation of radioactive seeds or local placement of a radioactive source into or near the targeted organ. IBRT can be given at a high dose rate (HDR) or low dose rate (LDR) with the difference being application time. HDR implants are placed for minutes to target

organs while LDR implants are placed for a longer period to continuously exude radioactivity until removed or depleted. One major advantage of brachytherapy is that the dose fall-off is exponentially faster, or, in other words, the gradient of radiation to tissues is much steeper so that there is less radiation exposure to surrounding normal tissues located further from the targeted organ. Thus, IBRT allows providers to apply a high therapeutic dose to malignant tissue to achieve favorable oncological outcomes while minimizing side effects.

Most female genitourinary malignancies such as cervical, uterine, and vaginal cancers are treated with a combination of both modalities. EBRT allows for broader regional control while brachytherapy delivers higher doses with more precise targeting.

Grading System

There are multiple published grading scales for radiation-induced toxicity including the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) system [1] and the LENT-SOMA (Late Effect of Normal Tissues/Subjective-Objective Management Analytic) [5]. Both of these grading systems were published in 1995 with the RTOG used for documentation outside the setting of a clinical trial (Table 1). The LENT-SOMA scoring system is far more detailed and integrates specific patient symptoms into account. Further, unlike the RTOG/EORTC system, the radiation changes to gynecologic structures are described and scored separately. Thus, this system is much more sensitive to the late symptomatic, structural, and functional disruptions experienced by patients after pelvic radiation therapy [5].

The most current and updated grading scale is the fifth version of the Common Terminology Criteria for Adverse Events (CTCAE) scales initially developed by the National Cancer Institute in 2003 [6]. The current fifth edition of the CTCAE is the primary platform to report toxicities in clinical trials. From a practical standpoint, however, this method of reporting is not generally used in clinical practice. Further within the urologic literature, the RTOG/EORTC grading still is most commonly used.

Organ-Based Radiation

The radiation dose of female pelvic malignancies can vary based on the targeted organ, radiation source (i.e., EBRT vs brachytherapy), cancer staging, and surgical candidacy. Therapeutic dosing must be framed within the context of the radiation tolerance of the normal surrounding tissues. In addition to the ability of normal tissues to withstand a total radiation dose, other contributing factors such as organ volume, fractionation schedule, and delivery mechanism weigh heavily into toxicity. Decades of literature relating radiation technique and complications resulted in one of the more comprehensive, though still incomplete, descriptions of radiation tolerance by organ by Emami et al. For example, the dosing correlating with a 50% chance of a bladder complication with 5 years is 80 Gy [7].

Per the National Comprehensive Cancer Network (NCCN) guidelines on cervical cancer [8], EBRT is an option for patients with stage IA1 with lymphovascular invasion or higher, either as definitive treatment or adjuvant in those with recurrent or metastatic disease. The targeted zone should at minimum cover the area of gross disease, uterosacral ligament, vaginal margin of 3 cm, parametria, and presacral nodes. For those at higher risk of nodal involvement, guidelines suggest including the pelvic and common iliac lymph nodes. Dosing for EBRT is approximately 45 Gy with an additional 10–20 Gy boost to areas of gross adenopathy. Brachytherapy at a dose of 5.5–6 Gy ×5 fractions can be used as definitive therapy with or without EBRT. If used in conjunction, the total dose for definitive treatment can range from 80 Gy for small tumors to > 85 Gy for larger volume tumors compared with a total dose of 45–50 Gy for adjuvant therapy.

For endometrial cancer, radiation is used as definitive treatment primarily in non-surgical candidates who have organ limiting disease or for those with extrauterine involvement. Otherwise, surgical extirpation is preferred. Radiation can also be used as adjuvant therapy after radical hysterectomy for any patients with stage IA histologic grade 2 or higher. Radiation doses for adjuvant dose and definitive therapy are similar to those of cervical cancer, ranging from 45 to 50 Gy [9].

Bladder cancer is typically treated surgically with either local resection or radical cystectomy for muscle invasive disease. Radiation can be a treatment option in bladder-sparing approaches to muscle invasive disease and targets the area between the mid-sacroiliac region and the upper limit of the common iliac artery bifurcation. The bladder is dosed with 40–50 Gy with additional boosts to locoregional pelvic lymph nodes for a total of 64–66 Gy [10]. For urethral cancer, the dose range is from 45 to 70 Gy for definite therapy, dependent on T staging [10].

First-line therapy for anal carcinoma remains surgical excision; however, chemoradiation can supplement treatment protocols if margins are positive or for locally advanced or metastatic cancer. Doses are typically 45 Gy in 1.8 Gy fraction for a total of 25 fractions. Grade 3–4 GU toxicities were noted in 1–2% of patients with preoperative chemoradiation therapy [11].

Colorectal cancer can be treated with neoadjuvant chemoradiation followed by surgical resection. Doses are 45–50 Gy in 25–28 fractions. Small bowel should be limited to a dose of 45 Gy, but for areas with positive margins, boosts of intraoperative radiation therapy or 10–20 Gy of EBRT can be considered [12].

Table 1 Grading systems of radiation-induced GU toxicities

Grade	CTCAE	RTOG—acute	RTOG—chronic	LENT-SOMA
0	No change	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)	Occasional or mild subjective symptoms*; > 2/3 normal vaginal length, superficial < 1 cm ulcer, asymptomatic vaginal dryness, patchy atrophy, telangiectasias without bleeding; managed with occasional non-narcotic/hormone cream/dilation, iron therapy
2	Moderate, local or non-invasive 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	Moderate frequency, generalized telangiectasia, intermittent macroscopic hematuria	Intermittent or intolerable subjective symptoms; 1/3–2/3 normal vaginal length, superficial > 1 cm ulcer, symptomatic dryness, confluent atrophy, telangiectasia with gross bleeding; managed with regular non-narcotic, intermittent hormone cream/dilation, occasional transfusion
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)	Persistent and intense subjective symptoms; < 1/3 normal vaginal length, deep ulcer, secondary dysfunction in vaginal dryness, non-confluent atrophy; managed with regular narcotic/hormone cream, frequent transfusions, persistent dilation
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 (< 1000 cc), severe hemorrhagic cystitis	Refractory and excruciating subjective symptoms; fistulae; obliterative vaginal length, diffuse atrophy; managed with surgical intervention
5	Death	Death	Death from uncontrolled hematuria	

*Subjective symptoms include dyspareunia, vaginal dryness, bleeding, and pain

Radiation-Induced Injuries

Lower Urinary Tract Symptoms and Voiding Dysfunction

Radiotherapy can result in bladder and urethral dysfunction secondary to the long-term interstitial fibrosis created by ROS. Analysis of 70 patients treated for cervical cancer treated with either chemoradiation or radical hysterectomy, those who underwent chemoradiation reported a higher, though not statistically significant, incidence of overall LUTS (77% vs 71.4%, $p = 0.78$) and storage symptoms (77.1% vs 62.9%, $p = 0.30$). Urodynamic parameters reveal those who underwent chemoradiation demonstrated poorer bladder compliance (mean 54.1 ± 43.3 ml/cmH_2O vs 71.3 ± 51.4 ml/cmH_2O, $p = 0.13$) , lower bladder capacity (mean 317 ± 122.9 ml vs 468 ± 129.3 ml, $p < 0.001$), and lower maximum flow rates (mean 17.8 ± 8.9 ml/s vs 18.4 ± 8.8 ml/s, $p = 0.78$). Of interest, there was a higher post-void residual in those who underwent surgical intervention (mean 47.6 ± 71.9 ml vs 7.7 ± 15 ml) [13].

Emirdar et al. demonstrated similar urodynamic information in their prospective study of 55 patients treated with radiotherapy for endometrial or cervical cancer. Patients were categorized into three groups: total abdominal hysterectomy (TAH) with adjuvant radiotherapy ($n = 10$); TAH, bilateral salpingo-oophorectomy, pelvic lymph node dissection; and omentectomy with adjuvant radiation ($n = 36$), or primary radiotherapy ($n = 9$). Bladder capacity decreased significantly for all groups with the range of change from 69 to 110 ml, most notably in group 2. Volume at normal and severe

urgency also changed significantly from 351 ml pre-treatment to 301 ml post-treatment for the former and 485 to 393 ml for the latter in group 2. However, other parameters such as incontinence, urethral mobility, first urge to urinate, post-void residual, and maximum detrusor pressure had no statistically significant difference. Notably, because the most substantial changes are seen in group 2 where surgical treatment is also the most aggressive and the radiation dose is the lowest (4963 ± 1357 Gy vs 6180 ± 278 Gy in group 1 vs 7093 ± 985 Gy in group 3), the authors postulate that a large attributing factor in the urodynamic changes is demonstrated in patients with combined surgical intervention. Conversely, a study by Roszak et al. comparing radiation toxicities in patients who underwent radiation ± chemotherapy vs surgery with adjuvant radiation for endometrial or cervical cancer suggest that radiation itself is a major risk factor for urinary and gastrointestinal injuries. Though 51.3% of patients ($n = 263$) developed early toxicity, those who underwent radiation ± chemotherapy alone had a higher incidence (27%) than those who underwent surgery with adjuvant radiation (24.3%) ($p < 0.007$). This pattern was the same for late toxicities (9.9% vs 4.9%, $p < 0.006$). Interestingly, there were higher incidences of GI than urinary toxicities in both early and late stages (33.1% and 13.3% vs 22.1% and 3%, respectively). Specifically for urinary symptoms, this study reported a higher incidence of grades 3 and 4 early toxicity in those with radiation (6.6%) or chemoradiation (10.4%) vs those who had adjuvant radiation (8% with cervical cancer, 1.5% with endometrial cancer) [14].

Changes in urinary symptoms for patients undergoing multimodality therapy for rectal cancer correlate with increased bother scores as described in a prospective study by Bregendahl and associates [15]. Using the International Consultation on Incontinence Modular Questionnaire–Female Lower Urinary Tract Symptoms (ICIQ-FLUTS), the authors demonstrated that 26.6% (total = 515) of female patients who underwent low anterior resection (LAR), abdominoperineal excision (APR), or total mesorectal excision (TME) with or without neoadjuvant radiation reported hesitancy with 15.2% reporting a moderate to severe bother score. In the 35.3% who reported interrupted stream, 12.7% described symptoms as moderately to severely bothersome, and, similarly, 20.2% reported straining with 21% having moderate to severe bothersome scores. Though surgical treatment is the predominant contributing factor in many cases, radiation was shown to exacerbate the voiding dysfunction (OR = 1.63, CI = 1.09–2.44). Another retrospective study of 11,068 rectal cancer patients using the Surveillance Epidemiology and End Results (SEER) database supports the impact of radiotherapy on LUTS [16•]. Upon evaluation of the urinary adverse effects after surgery alone or surgery with neoadjuvant/adjuvant radiation, the authors found that patients with combined therapy had a higher incidence of urinary adverse effects (12.19–14.23% vs 10.17–13.39%) at 2, 5, and 10 years with rates increasing with time (HR = 1.28, 95% CI = 1.16–1.40; $p < 0.0001$). More specifically, these adverse effects include incontinence (2.9–3% vs 2.3–2.9%), cystitis/spasm/hematuria (2.4–3.5% vs 2–2.2%), and retention (8–10.4% vs 8.2–10.5%).

The prevalence of urinary symptoms is variable but can be dramatic in patients previously treated with radiation for endometrial cancer. In a study by de Boer et al. [17•], analysis of results of the Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-2 trial for long-term bladder and bowel function in patients who underwent either external beam radiotherapy (EBRT) or vaginal brachytherapy (VBT) for endometrial cancer was performed. As captured via the HRQL questionnaire, urinary symptoms, such as nocturia (35.3%), urinary urgency (32.7%), and incontinence (20.8%), all increased from baseline and continued to worsen with time at 84 months (median follow-up = 65 months). However, there was a decrease from the baseline for frequency (36.5%) and dysuria (7.9%) to 32% and 3.2% at 84 months post-treatment, respectively. This trend is reiterated in the study by Klopp et al. where they reported in increased urinary symptoms via the EPIC questionnaire in patients with either standard RT or IMRT for endometrial or cervical cancer [18••].

In contrast, a study by the Gynecologic Oncology Group showed that despite 43% of patients reporting low grade GU toxicity, only 2–5% had severe symptoms [19••]. Moreover, in a prospective study on the BC2001 protocol, grades 3–5 genitourinary toxicity in radiation, only bladder cancer patients treated with radiation only were 32% and 21% at a median follow-up of 36 and 69 months, respectively [20]. These toxicities can include hemorrhagic cystitis, lower urinary tract symptoms, urinary incontinence from sphincteric deficiency, and vesical fistulas which will be discussed in detail below.

Hemorrhagic Cystitis

The pathophysiology of hemorrhagic cystitis begins with initial tissue edema induced by ROS which subsequently develops into telangiectasia and interstitial fibrosis of the submucosal arteries. This process potentiates tissue hypoxia (Fig. 1). As a result, progressive obliterative endarteritis leads to mucosal ulceration and gross hematuria. Fibrosis also leads to the reduction of bladder capacity and compliance so that patients often report gross hematuria with or without clot retention, urinary urgency, frequency, and dysuria. Median time to presentation can range from 6 months to 10 years; however, such symptoms can occur decades after treatment. The incidence of radiation cystitis is estimated to be 5% based on a 2016 study by Zwaans et al. [21], but it is a diagnosis of exclusion; thus, infectious (viral and bacterial), coagulopathy, and malignant causes must be ruled out with appropriate imaging, laboratory analysis, and cystoscopy.

Fig. 1 Radiation cystitis. Severe radiation cystitis with areas of telangiectasias and patches of yellow necrosis as seen on cystoscopy

Selection of treatment options for hemorrhagic cystitis is proportional to the severity of symptoms. Initial measures include conservative management with hydration with or without continuous bladder irrigation (CBI) [22]. Cystoscopy with clot evacuation and fulguration can be attempted if CBI is unable to control the bleeding or if complete clot evacuation is inadequate with the catheter.

For intractable hematuria, intravesical instillation of various agents can be attempted which include alum and formalin. In general, these intravesical agents may be useful in certain clinical situations; however, they must be used judiciously, primarily with regards to formalin, as unintended consequences may include inadvertent ureteral reflux and vesical fibrosis.

Another option for persistent hematuria is hyperbaric oxygen therapy (HBOT), a therapy first described in 1985 [23]. Since tissue hypoxia is one of the instigators of hemorrhagic cystitis, delivery of oxygen to the tissue should theoretically improve neovascularization and wound healing. For drastic situations, more invasive maneuvers such as bladder embolization, supravesical diversion or even simple cystectomy, and urinary diversion can be considered.

Selective embolization of the hypogastric artery or the anterior branch of the internal iliac can be attempted by interventional radiology. Careful attention must be made to preserve the superior gluteal artery as occlusion of this may lead to significant gluteal pain. For supravesical diversions, the object is to divert the urine which contains urokinase, a thrombolytic enzyme naturally secreted in the urine, to allow for hemostasis in the bladder. This can be accomplished using percutaneous nephrostomy tubes with or without ureteral occlusion. An intact bladder will continue to shed mucosal epithelium or continue to bleed which raises the risk of pyocystis (67%), hemorrhage (23%), and severe pain (13%). In extreme situations, a vesicovaginostomy for cervical cancer survivors has been employed as an option. As a last resort, a simple cystectomy with urinary diversion is a therapeutic solution for select patients [24].

Urinary Fistulae

After radiation, fistulae may develop between any components of the urinary tract—ureters, bladder, or urethra—and surrounding organs, such as the vagina and bowel (Figs. 2 and 3). In a retrospective study evaluating the rate of fistula repair in cervical cancer patients treated with either radiation, surgery, or both, the authors reported an incidence of 0.9% of patients developing and requiring surgical repair of a urinary fistula [25]. The median time from radiation therapy to fistula development is in general approximately 20 months [26]. Risk factors for fistulas include hysterectomy, prior pelvic surgery, endometriosis, diabetes, hypertension, cancer with bladder involvement, or radiation therapy for greater 6 weeks [26, 27]. It is of utmost importance to rule out recurrent malignancy at the site of the fistula before proceeding with any surgical treatment.

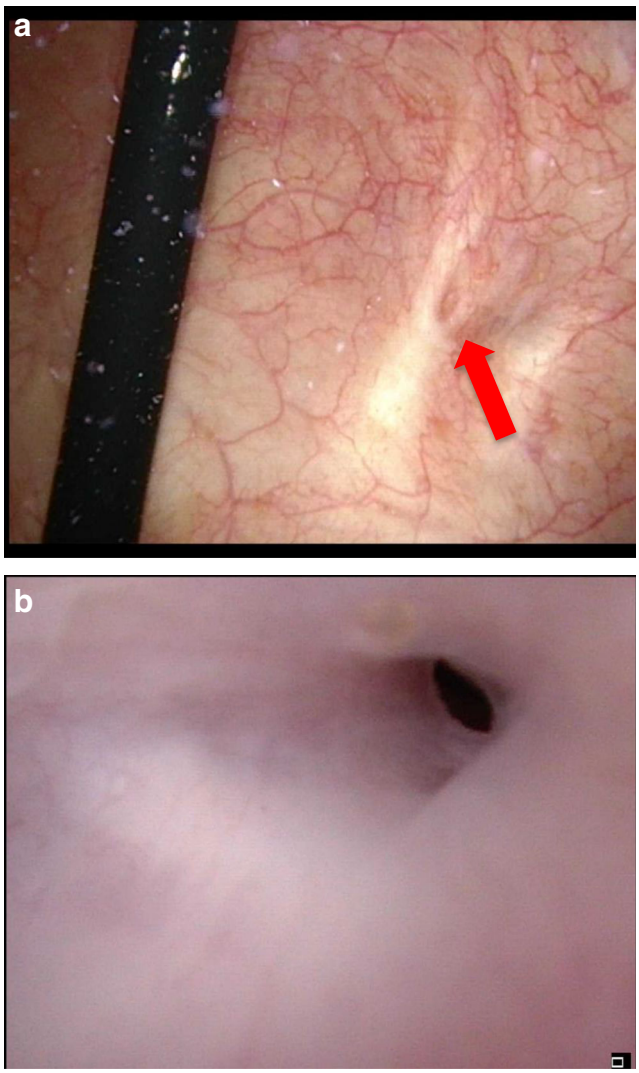

Fig. 2 Small vesicovaginal fistula. **a** Cystoscopy shows a small left posterior wall fistula (red arrow). **b** The same fistula is demonstrated from a colposcopy view

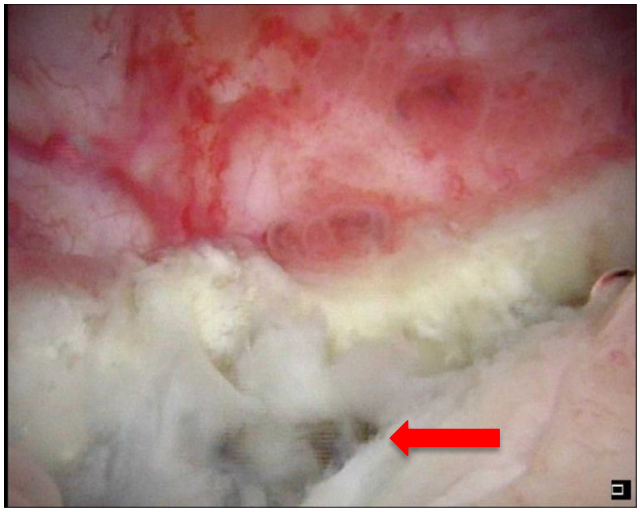

Fig. 3 Large vesicovaginal fistula located posterior to the trigone associated with extensive fibrosis and necrosis (red arrow)

For minor fistulas, urinary diversion with an indwelling catheter or fulguration of the tract may successfully resolve the issue [27]. For some, surgical repair with muscle interposition, Martius or omental flaps are indicated. The risk of failure is much higher in post-radiation patients. In a study of patients with either entero-urinary or urinary cutaneous fistula, 32 of the 44 radiated patients required permanent diversion because of the failure rate vs 3 out of the 42 non-radiated patients ($P < 0.0001$) [28].

Ureteral Strictures

Periurethral fibrosis, atrophy, and subsequent tissue contraction contribute to the development of strictures which can occur in the ureters, bladder neck, or urethra.

Ureteral strictures have been estimated to be 5% in patients with adjuvant radiation compared with 2.5% in patients with radiation as primary treatment [19••]. Other studies have estimated ureteral strictures to be as low as 1.2% at 10 years and 2.5% at 20 years to as high as 10.3% in patients with radiation as a curative measure for cervical cancer [25, 29]. In one study, ureteral strictures were the most common radiation-induced complication for cervical cancer treatment (18/134 pts; 13.4%) [30]. Distal ureteral strictures are more prevalent than mid, proximal, or pan-ureteral strictures (65.2% vs 8.7% vs 0% vs 8.7%) in those with previous radiation as compared with non-irradiated ureteral strictures (29.6% vs 22.2% vs 24.7% vs 7.4%, $p = 0.006$) [31•]. Similar to fistulas, it is important to rule out recurrent disease at site of stricture before proceeding with treatment. There are a variety of surgical treatments for ureteral strictures ranging from endoscopic management with percutaneous nephrostomy, ureteral dilation or incision, or chronic indwelling stents to complicated ureteral implantation, ureteroureterostomy, ileal ureter, or autotransplantation [31•]. Certain challenges exist because of the nature of radiation-induced injuries while performing repairs, especially the effect of decreased vascularity of the tissue on the healing of anastomoses. However, Monn et al. reported that patients with radiation-induced strictures who underwent an ileal ureter repair did not have a higher risk of anastomotic stricture than non-irradiated patients (0%, $n = 23$ vs 2.25%, $n = 81$) [31•]. There were higher rates of hyperchloremic metabolic acidosis (8.7% vs 1.2%, $p = 0.122$), renal failure requiring dialysis (4.3% vs 1.2%, $p = 0.395$), fistulas (13% vs 3.7%, $p = 0.095$), and partial small bowel obstruction (21.7% vs 7.4%, $p = 0.063$) in previously radiated patients though. Others report a stricture rate of 4.08% in those who underwent extravesical reimplantation for radiation-induced distal ureteral strictures and 4.44% in those with Boari flap ureteroneocystostomy [32].

Conclusion

Although the utilization of radiation therapy ushered in a promising era for cancer treatment, there are urinary tract complications which can occur acutely or with a latency period of decades. While the effect on the quality of life may range from mild to devastating, these adverse events may require long-term conservative management to complicated surgical treatment. A critical component of patient care is a thoroughly discussion of possible genitourinary complications in pre-treatment counseling. However, as the sequelae of radiation treatment may be spread over decades from the initial therapy, reinforcement of these possibilities are necessary throughout the entire survivorship phase.

Compliance with Ethical Standards

Conflict of Interest Dr. Hoang and Dr. Ajay declare they have no conflict of interest. Dr. Westney is a consultant for Boston Scientific.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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