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Pelvic Radiation Disease

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Abstract

Pelvic radiation is increasingly being used for the neoadjuvant and definitive treatment of pelvic organ malignancy. While this treatment can be highly effective, and may assist in organ sparing, it is also associated with significant toxicity and devastating adverse events that need to be considered. In broad terms, pelvic radiation disease affects both the primary target organ as well as adjacent organs and soft tissue structures, with complications that can be classified and graded according to consensus criteria. The complication grade is often modality, dose, and area dependent. The most common manifestations are proctitis, cystitis, recto-urethral fistula, ureteric stricture, and bone involvement. Toxicity can be misdiagnosed for many years, resulting in significant management delays. Complications can be difficult to prevent and challenging to treat, requiring specialized multi-disciplinary input to achieve the best possible strategy to minimize impact and improve patient quality of life.

Keywords
- pelvic radiation
- radiation proctitis
- radiotherapy
- recto-urethral fistula
- osteonecrosis

Ionizing radiation therapy has been used in the armamentarium of cancer treatment for a few decades. Radiation therapy works by damaging the DNA of cancer cells through either direct or indirect ionization, relying on precise treatment targeting and differential healing to minimize injury to surrounding tissues relative to the tumor. Pelvic radiotherapy is most commonly utilized in the treatment of prostate cancer, gynecological malignancy, and anorectal cancer, with increasing focus on organ preservation in more recent years resulting in an increase in the rate of use of radiation in both the neoadjuvant and definitive treatment settings.[1]

Generally, there are two modes of delivery of ionizing radiation: external beam radiotherapy, and internal delivery mechanisms such as brachytherapy (BT). However, several recent advances in technology have served to increase efficacy and reduce toxicity of radiotherapy administration.[2] These include three-dimensional conformal radiotherapy (3D-CRT), intensity-modulated therapy, volumetric-modulated arc therapy which effectively allow shaping of the radiation dose to the three-dimensional shape of the tumor target, and variation of the intensity of the radiation dose to spare normal tissue as much as possible.[2] Proton beam therapy allows better delivery of radiation intensity to the target area, up to a maximum that occurs near the end of the particle's range (the Bragg peak), again depositing even less energy in surrounding healthy tissue.[3]

Despite all of these advances, however, radiation-induced toxicity, side effects, f profile.[4,5] With pelvic radiation therapy, the risks are well defined by anatomical boundaries, and classification and grading of complications are defined by consensus guidelines (►**Table 1**).[5] The aim of this narrative review is to focus on practical identification and management of the more common presentations of pelvic radiation disease.

Proctitis

Presentation

Acute radiation proctitis is defined as occurring within 3 months of treatment delivery, and reflects the acute inflammatory process involving the superficial rectal mucosa (►**Fig. 1**).[6] This is a common adverse event of pelvic radiation (up to 75% of patients in early series).[7] The most common presenting symptom is diarrhea, which is typically

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Table 1 Gastrointestinal and genitourinary complications according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) morbidity scale and the Common Terminology Criteria for Adverse Events (CTCAE) v4.03

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Gastrointestinal (bowel)					
RTOG/EORTC					
Acute	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics.	Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics.	Diarrhea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops).	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion.	Death
Late	Mild diarrhea; mild cramping; bowel movement five times daily; slight rectal discharge or bleeding.	Moderate diarrhea and colic; bowel movement more than five times daily; excessive rectal mucus or intermittent bleeding.	Obstruction or bleeding, requiring surgery.	Necrosis/perforation fistula	Death
CTCAE V4.03					
Rectal bleeding	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated.	Transfusion, radiologic, endoscopic, or elective operative intervention indicated.	Life-threatening consequences; urgent intervention indicated.	Death
Ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea).	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling.	Life-threatening consequences; urgent operative intervention indicated.	Death
Fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function.	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated.	Life-threatening consequences; urgent intervention indicated.	Death
Genitourinary (bladder)					
RTOG/EORTC					
Acute	Frequency of urination or nocturia twice pretreatment habit/ dysuria, urgency not requiring medication.	Frequency of urination or nocturia that is less frequent than every hour; dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium).	Frequency with urgency and nocturia hourly or more frequently/dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/without clot passage.	Hematuria requiring transfusion/acute bladder obstruction not secondary to clot passage, ulceration, or necrosis.	Death

(*Continued*)

Table 1 (*Continued*)

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Gastrointestinal (bowel)					
Late	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria).	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria.	Severe frequency and dysuria; severe telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (<150 mL).	Necrosis/contracted bladder (capacity <100 cc); severe hemorrhagic cystitis.	Death
CTCAE V4.03					
Haematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated.	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL.	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective endoscopic, radiologic, or operative intervention indicated; limiting self-care	Life-threatening consequences; urgent radiologic or operative intervention indicated.	Death
Urinary Fistula	–	Noninvasive intervention indicated; urinary or suprapubic catheter placement indicated.	Limiting self-care; elective radiologic, endoscopic, or operative intervention indicated; permanent urinary diversion indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated.	Death
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only.	Symptomatic but no hydronephrosis, sepsis, or renal dysfunction; urethral dilation, urinary, or suprapubic catheter indicated.	Symptomatic and altered organ function (e.g., hydronephrosis or renal dysfunction); elective radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated.	Death

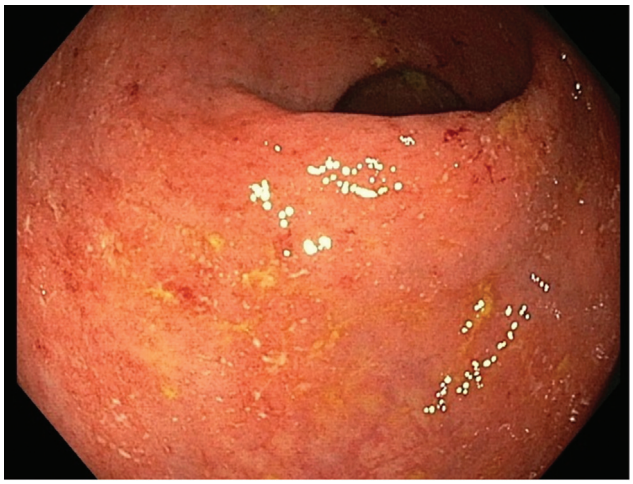

Fig. 1 Endoscopic image of radiation proctitis.

self-limiting once treatment is ceased or completed. Significant bleeding requiring intervention is rare, and perforation is very rare in the acute setting unless related to rectal cancer treatment response or progression.

Chronic radiation proctitis is fortunately less common. The incidence of clinically significant hemorrhagic proctitis is approximately 5% over 5 years (or 1% per year), with most patients manifesting symptoms within 2 years after radiotherapy for prostate cancer (which remains the most common cause).[5] Patients with chronic radiation proctitis can present acutely with large volume rectal outlet type bleeding or in an outpatient setting with low volume bleeding or iron deficiency anemia. The cause for this bleeding is development of abnormal angiogenesis in the superficial layer of the lamina propria of the rectum, due to radiation-induced ischemia and fibrosis in the submucosa.[8] Thus, the diagnosis is typically made on colonoscopy to exclude other pathology, with characteristic macroscopic appearance. Biopsy is not usually required.

Management

The management of acute proctitis is typically watchful waiting and supportive therapy, as the symptoms typically subside when the treatment is completed. In more severe cases, treatment may have to be stopped.

There are several options for the treatment of chronic proctitis, some more successful than others at resolving symptoms.[6] In practice, Argon plasma coagulation (APC) delivered by colonoscopy or flexible sigmoidoscopy is probably the current standard of care in the initial treatment of chronic radiation proctitis due to its safety and efficacy at ablating the abnormal bleeding vasculature.[9] Multiple treatments may be required. Formalin 4% topical instillation is also effective (arguably more so) but associated with a higher risk of significant local complications.[10,11] Its use is typically reserved for the treatment of larger areas of proctitis where serial APC application has failed. Other medical treatments such as sucralfate enemas and oral antibiotics are considered potential adjuncts but are not in common use in clinical practice.[5,12]

In patients where topical ablative treatments have failed, hyperbaric oxygen (HBO) and surgical resection need to be considered.[13] HBO is effective, but use is often limited by issues of access and cost.[14] Surgery is usually reserved for patients with highly significant and debilitating bleeding, stricture, or fistula (see below) due to very high morbidity and mortality rates.[11] The ideal surgical approach, in particular the question of simple diversion versus formal resection, remains unclear.

Cystitis

Presentation

Similar to radiation proctitis, cystitis can also occur and is one of the most common complications of pelvic radiotherapy with an incidence ranging from 20 to 80% depending on dose, fields, and method used.[5,15] The pathophysiology is similar to radiation in proctitis in that tissue ischemia, necrosis, and fibroblast deposition result in compensatory abnormal superficial neovascularization with a tendency for this to be friable and easily damaged resulting in bleeding. The incidence of severe hematuria ranges from 5 to 8%.[15] Patient risk factors for more severe hemorrhagic cystitis include a prostate volume of $>40\,cm^3$ and being on anticoagulants.[5]

Management

A practical algorithm for the management of radiation-induced severe hemorrhagic cystitis was recently published by Pascoe et al.[16] In the acute setting, management typically requires initial resuscitation, reversal of anticoagulation, catheterization with a three-way indwelling catheter followed by bladder washout with clot evacuation and continuous bladder irrigation.[16] Cystoscopy and manual clot evacuation and electrocoagulation (cystodiathermy) or other form of laser coagulation such as yttrium-aluminum-garnet (YAG) or KTP "Greenlight" laser may be needed (Ref #5). For severe bleeding tranexamic acid sometimes used as an adjunct, although data for efficacy is limited.[16] Most often the bleeding will be self-remitting and settle spontaneously. Intravesical therapy with aluminum salt irrigation (Alum), formalin, or glycosaminoglycan replacement has been used historically with limited benefits and long-term success.[17] These are used in patients refractory to nonoperative treatment. Consolidative therapy with HBO is strongly recommended and is more commonly used than for radiation proctitis.[16] A recent systematic review showed overall and complete response rates of 87 and 65%, respectively, but use may be limited by issues of access and cost.[18] Unfortunately long-term durability data are limited.

Surgical urinary diversion with an ileal conduit (with or without cystectomy) is considered a last resort as it is associated with very high morbidity and mortality rates in this setting, likely because the ureters are also irradiated and wound healing is therefore compromised.[19]

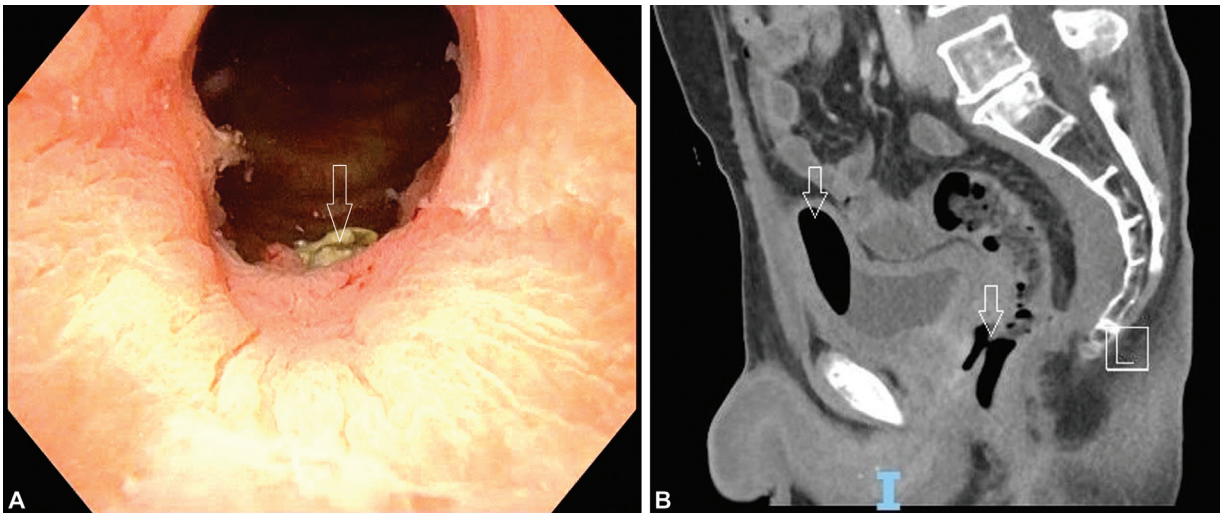

Fig. 2 (**A**) Image of a Rectourethral fistula via cystoscopy (arrow points to the fistula). (**B**) CT image of a rectourethral fistula (left arrow points to air in the bladder and right arrow points to the fistula).

Rectourethral Fistula

Presentation

Compared with proctitis and cystitis, the incidence of rectourethral fistula (RUF) after pelvic radiotherapy is low. However, the prevalence of RUF is rising with the increasing use of radiation in the treatment of prostate cancer (the incidence of RUF is approximately 0.3% after BT for this indication).[5] Another at risk group are male patients with low, anteriorly based locally advanced rectal cancer that have undergone neoadjuvant radiation and surgery (due to iatrogenic urethral injury in an irradiated field). The symptoms of RUF can be debilitating with urine discharge through the anus, and pelvic sepsis in some cases (►**Fig. 2**).

Management

Referral to a tertiary center with specific expertise is recommended because the treatment can be extremely challenging, nonoperative options are limited, and surgical options are complex.[20] A detailed algorithm for management was proposed by one such expert center in 2014,[21,22] and a simpler one published in a prior systematic review.[20] Initial diagnostic tests include cystoscopy, urethrogram, and urodynamic studies are undertaken to assess anatomy and determine bladder capacity. Biopsies are required to exclude malignancy. Flexible sigmoidoscopy is also performed to assess the rectum and exclude a secondary rectal malignancy or recurrence. An MRI pelvis is useful to visualize adjacent structures, and a surveillance/stage CT or PET is often performed to assess for any distant metastatic disease, prior to undertaking any surgery. The Martini Staging System is used to classify and grade RUF. Radiation-related RUFs are defined as Grade 1 according to these criteria but are further subdivided into Stage I if diameter is <1.5 cm, Stage II if diameter >1.5 cm, and Stage III if there is urethral sphincter damage regardless of size.[23,24]

Once the initial assessment is complete, a multidisciplinary surgical plan is formulated. Initial management typically involves urinary (urethral and suprapubic catheter) as well colostomy diversion for up to 6 months.[22] During this period, treatment of pelvic sepsis, nutrition optimization, and HBO therapy can be useful to aid in tissue healing. Once this period of diversion is complete, cystoscopy is repeated to re-stage the fistula and plan further surgery. Depending on anatomy and patient status a transabdominal, transanal, trans-sphincteric or trans-perineal approach may be chosen. Typically defect repair is supplemented with a buccal mucosal flap and/or a local vascularized rotation pedicled flap (most commonly gracilis muscle rotation). Success rates in expert centers performing trans-perineal flap repairs approach 90% and this is the preferred approach in most cases of small/medium fistulae (►**Fig. 3**).[20,25] Ultimately, however, if the defect is too large to repair (greater than 3 cm) or if the initial repair is unsuccessful, either permanent diversion or total pelvic exenteration are discussed with the patient as a last resort but with definitive form of surgical treament.[20,25]

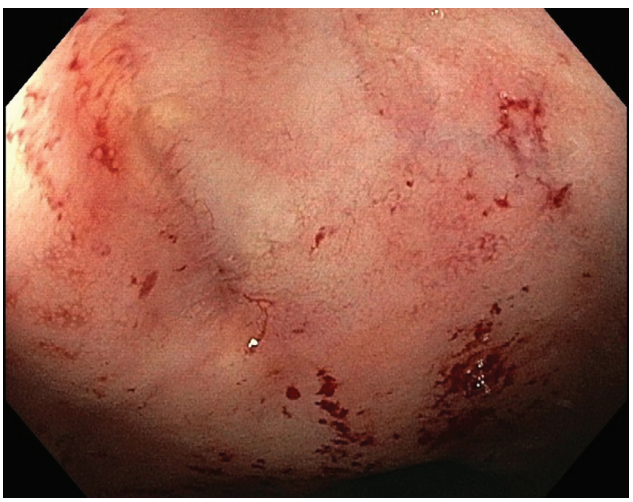

Fig. 3 Endoscopic image of a healed rectourethral fistula following repair with buccal mucosal flap.

Ureteric Stricture

Presentation

Clinically significant distal ureteric strictures after pelvic radiation have an incidence of approximately 1 to 2% over 10 years and are more commonly seen in patients who have also had pelvic surgery before or after radiation was administered.[5] Patient present with flank pain, upper tract urinary infection, and deterioration of renal function, or when proximal hydronephrosis is detected on surveillance imaging.

Management

Temporizing management involves cystoscopic ureteric stent placement and reassessment of the renal unit function. Definitive management depends on the segment of the ureter involved, health of the other pelvic organs including bladder, and overall renal unit function. Surgical resection and re-implantation of the affected ureter using a bladder flap technique, or ileal interposition depends on length of healthy ureter available.[26] In refractory cases, or those that have failed initial attempts, or have complicating issues reconstruction, diversion or nephrectomy may be required.

Osteonecrosis

Presentation

While sporadic reports historically touched on problems related to the pelvic bones after definitive therapy for pelvic malignancies with radiotherapy, there is still a paucity of data about bone involvement. Any part of the bony pelvis can be involved, with the most commonly recognized being the hip acetabular joint,[27–29] but pubic symphysis involvement is also common and until recently has been grossly under-recognized. The first report was published in 1998 by radiologists,[30] and then finally recognized as a clinical entity by surgeons in 2002.[31] Radio-ablative energy is hypothesized to cause (in a stepwise progressive fashion from least to most severe): osteonecrosis, concomitant bladder neck injury, urinary extravasation, acute osteomyelitis, and finally development of a mature urinary pubic symphysis fistula with chronic osteomyelitis.[32]

Pelvic pain and/or difficulty with ambulation are the typically reported symptoms. Pain is usually insidious in onset and tends to result in management delays. In the most severe cases anterior and posterior involvement ensues, leading to ischial involvement, adductor compartment involvement, abscess formation and eventual cutaneous fistulae. Depending on the complexity other complications such as recurrent urinary tract infections, cutaneous or rectal fistulae, thigh and pelvic abscess may be seen as well.[33]

Management

The management of hip joint radionecrosis is typically analgesia and physiotherapy, with total hip arthroplasty or resection arthroplasty used for definitive treatment.[28] Management of advanced pubic symphysis disease or fistulae is more complex. In the majority of cases, intravenous antibiotics, percutaneous drainage of abscess, urinary drainage with penile or suprapubic catheter, and fecal diversion (where appropriate) have been utilized as a temporizing measure or for the long-term management in surgically unfit patient.[34] Patients looking for -term resolution should then be managed with optimized nutrition, and counselling toward major surgery similar to the RUF algorithms above. For anterior pelvic bone fistulae, durable outcomes are seen following extirpative surgery with a cystectomy, loop urinary diversion, and complete pubic symphysis resection, often resulting in marked improvement in pain and function.[34,35] If the rectum is involved, total pelvic exenteration is needed.

Sexual Dysfunction

Presentation

Post radiotherapy sexual dysfunction is also an under-recognized complication, and often difficult to separate from the effects of surgery and the primary disease process.[36,37] Symptoms include decreased libido, reduced arousal, difficulty achieving orgasm, erectile and ejaculatory dysfunction in men, and dyspareunia and vaginal dryness in women.[38] Poor overall satisfaction with intercourse is also reported.[39]

Management

Advances in treatment targeting, and minimization of radiation dose using adjuncts like vaginal dilators and prostate-rectal spacers have a role in reducing the impact of radiation on sexual function through mitigating sexual organ toxicity.[40] However, more patient reported outcome data are required to better understand the problem and investigate options for prevention and treatment.[41,42]

Currently management mainly takes the form of pre and post-treatment sexual health counselling,[43] pelvic floor physiotherapy, and vaginal dilators in women,[44,45] and sexual aids such as phosphodiesterase 5 inhibitors in men, to improve sexual function.[46] Ideally counselling and interventions should be undertaken at a dedicated multi-disciplinary sexual health clinic,[43] including specifically trained oncology nurses providing psychological and practical support.

Summary

Radiation-induced pelvic toxicity can be devastating and will seldom present with a single organ injury. If there is a clinical indication to do so, the practitioner should actively look for other areas of pelvic or abdominal involvement, prior to embarking along the long path toward symptom resolution. Complete resolution with conservative management is often near impossible and temporizing measures are available to improve the quality of life in the first instance. Ultimately, surgical management may be required in more advanced and treatment-resistant disease. As this surgery is complex and often a last resort, management should occur in a specialized multi-disciplinary environment including dietetics, hyperbaric oxygen, and infectious disease physicians, and colorectal/urological/plastic surgeons and with shared decision-making approach to achieve optimal outcomes.

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