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Radiation Cystitis: a Contemporary Review

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Abstract

Purpose of Review There is not a universally agreed upon treatment algorithm for radiation cystitis. The goal of this review will be to discuss numerous options available to the provider at various points in treatment and the literature supporting its use.

Recent Findings There are various degrees of presentation, with milder forms that can be managed as outpatient and more serious forms requiring inpatient admission. There are a myriad of treatment options, including intravesical instillations, ablative procedures, systemic therapies, hyperbaric oxygen therapy, arterial embolization, and urinary diversion. If these measures are able to control the bleeding in the acute setting, the patient can then be considered for outpatient systemic therapy to decrease the risk of hematuria recurrence. Hyperbaric oxygen therapy has emerged as an outpatient treatment option with very promising results; however, further research needs to evaluate its long-term cost-effectiveness.

Summary Radiation cystitis is a devastating disease process that can occur months to years following radiotherapy and poses many therapeutic challenges. When conservative measures fail to control bladder hemorrhage, arterial embolization or urinary diversion may be ultimately necessary as life-saving measures, however, these are associated with considerable morbidity and mortality. Due to the devastating impact of radiation cystitis on patient quality of life, further research is imperative in order to add further innovative treatment strategies to our armamentarium.

Keywords Radiation cystitis · Hemorrhagic cystitis · Radiation-induced hematuria · Bladder hemorrhage · Radiation bladder injury

Introduction

Radiation therapy is a commonly used treatment modality in the management of pelvic malignancies including prostate and cervical cancers, and less commonly bladder, ovarian, uterine, vulvar, and colon cancers. Radiotherapy can affect not only the targeted tissue but also the surrounding tissue leading to the development of potential side effects. Radiation cystitis is one side effect that can develop months to years following radiation therapy that may be devastating for the patient and challenging for the urologist to treat.

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Epidemiology

Among patients receiving pelvic radiation, the incidence of radiation cystitis varies from 23 to 80% [1]. This wide range is likely due to several factors including (1) varying definitions of the disease, (2) differences in rates of the acute and chronic forms of the disease, (3) variable follow-up intervals across different studies, and (4) variable radiation dosing schedules and modes of delivery [1]. The average amount of time between radiation therapy and onset of symptoms is 31.8 months [1]. Males are more likely than females to develop the disease, with a male to female ratio of 2.8:1 [1]. The higher observed rate in the male population is believed to be secondary to the frequent use of radiation in the treatment of prostate cancer [1]. Chronic hemorrhagic cystitis, defined as chronic intermittent bleeding from the inflamed bladder mucosa, occurs in up to 5–10% of patients following pelvic radiation, and can occur up to 14 years following radiation therapy [1, 2].

Pathophysiology and Clinical Presentation

The underlying pathophysiology of radiation cystitis can be subdivided into acute and chronic phases. The acute phase, which occurs within 6 months after radiation treatment, involves the disruption of cellular tight junctions and the glycosaminoglycan (GAG) polysaccharide layer in the urothelium resulting in urothelial permeability to hypertonic urine and subsequent tissue inflammation and edema [1]. It has been postulated that the leakage of potassium ions into the bladder interstitium causes the activation of C-fibers, release of substance P, and a subsequent neuroinflammatory cascade involving mast cell activation and histamine release [3]. Clinically, the acute phase may manifest with lower urinary tract symptoms including urinary urgency, urinary frequency, dysuria, and hematuria. Cystoscopy may demonstrate erythematous and friable bladder mucosa with telangiectasias [2]. The telangiectasias develop secondary to haphazard neovascularization, and make the bladder mucosa prone to bleeding. The development of acute cystitis following radiation has been shown to involve a variety of inflammatory factors. Giglio et al. demonstrated a decrease in the expression of Toll-like-receptor-4 (TLR4) and interleukin IL-6 within the urothelium, and an increase in IL-10 in the connective tissue of the submucosa in response to radiation in a rat model [4]. A decrease in IL-6 was also detected in the urine, suggesting impaired TLR4-dependent IL-6 secretion from the urothelium [4]. IL-10 has previously been implicated as an important cytokine in the Th2-mediated immune response [5]. They also noted decreased nitrite levels in the urine, suggesting decreased release of nitric oxide into the urine in response to radiation [4].

The chronic phase, which manifests between 6 months and 20 years following radiation therapy, involves radiation-induced vascular injury wherein an obliterating endarteritis develops secondary to fibrosis of the submucosal arterioles and capillaries leading to tissue hypoxia, ischemia, and necrosis [2]. Bladder fibrosis develops in a delayed fashion, in which the smooth muscle fibers of the bladder are replaced with fibroblasts and collagen and reduction in bladder compliance and capacity ensues [1]. The chronic phase may present with symptoms such as urinary urgency, urinary frequency, dysuria, hematuria, incontinence, decreased bladder capacity, ulceration of the bladder mucosa, and possible bladder perforation and fistula formation [6].

The Radiation Therapy Oncology Group (RTOG) has a grading system for radiation cystitis (Table 1). For hematuria, the National Cancer Institute published a similar grading system (Table 2). An alternative clinical grading system for hematuria, first introduced by De Vries and Freiha, is also commonly used and suggests there are various degrees of presentation: (1) Mild: no transfusion requirement, does not warrant hospital admission; (2) Moderate: 1–6 units transfused; (3) Severe: > 6 units transfused [7].

Diagnosis

Initial work-up involves a complete history and physical exam. Specific attention should be paid to the patient's oncologic history, in addition to the timing and duration of any past radiation therapy. Urinalysis and urine culture should be obtained to rule out any infectious etiologies of the patient's symptoms. The presence of macroscopic (gross) or microscopic hematuria (≥ 3 RBC/hpf) should prompt further evaluation with upper tract imaging (CT/MR urogram or retrograde pyelography), cystoscopy, and possibly urine cytology depending upon the patient's age and risk factors.

Acute Inpatient Management

There is not a universally agreed upon treatment algorithm for radiation cystitis. The goal of this chapter will be to discuss numerous options available to the provider at various points in treatment and the literature supporting its use. Initial management strategies include adequate IV fluid resuscitation and a complete laboratory work-up consisting of a complete blood count, basic metabolic panel, INR, and urinalysis (Fig. 1). The patient's hematocrit should be monitored closely and transfusions given as needed. There should be cessation and/or reversal of anticoagulation if the risks of hemorrhage exceed the risks of coagulation. A postvoid residual should be checked to ensure adequate bladder emptying. If there is evidence of urinary retention, a large caliber intravesical catheter should be placed with aggressive manual irrigation for clot evacuation. If the bleeding is profuse, continuous bladder irrigation (CBI) should be initiated.

Cases with persistent hematuria despite CBI, often with various intravesical treatments, are typically taken to the operating room for cystoscopy, clot evacuation, and fulguration. Bladder biopsies may be performed if there is suspicion of underlying malignancy. The patient may require multiple trips to the operating room for control of bleeding. If attempts at electrocautery are futile, other ablative options include argon beam coagulation, GreenLight laser, and neodymium-doped yttrium aluminum garnet (Nd:Yag) laser. There are also various intravesical instillations that can be tried including

Table 1 RTOG grading system for radiation cystitis

Grade 1	Slight epithelial atrophy, minor telangiectasia, microscopic hematuria
Grade 2	Moderate urinary frequency, generalized telangiectasia, intermittent macroscopic hematuria
Grade 3	Severe urinary frequency and dysuria, severe generalized telangiectasia (often with petechiae), frequent hematuria, reduction in bladder capacity (< 150 cc)
Grade 4	Necrosis/contracted bladder (capacity < 100 cc), severe hemorrhagic cystitis
Grade 5	Death

aluminum ammonium sulfate or aluminum potassium sulfate (alum) aluminum, aminocaproic acid (amicar), botulinum toxin, fibrin glue, formalin, hyaluronic acid, and chondroitin sulfate. If these measures are able to control the bleeding in the acute setting, the patient can then be considered for outpatient systemic therapy to decrease the risk of hematuria recurrence. These options include aminocaproic acid (amicar), conjugated estrogens (Premarin), hyperbaric oxygen, and sodium pentosan polyphosphate.

In cases of refractory hematuria despite multiple attempts at intravesical instillations and fulguration/ablation, they may proceed to interventional radiology for either arterial embolization or percutaneous nephrostomy tube placement [8•, 9–12]. If this is unsuccessful, the last resort is surgical intervention.

Intravesical Therapies

Alum (Aluminum Ammonium Sulfate or Aluminum Potassium Sulfate)

Alum (aluminum ammonium sulfate or aluminum potassium sulfate) decreases bleeding by inducing vasoconstriction and reducing capillary permeability in response to the precipitation of proteins in the cell membranes and interstitium [13•]. It is typically administered via continuous bladder irrigation as a 1% alum solution [14]. The main difficulty that can be encountered when using this mode of delivery is that a colloid-like precipitate can form that can obstruct the catheter [14]. Hence, these patients must be monitored very closely to prevent overdistention of the bladder in a situation with a clogged catheter and high infusion rate.

Although it is not as effective as formalin, it is preferred for its better side effect profile. It is generally very well-tolerated, with bladder spasms being the most common observed side effect in 35% of patients [13•]. Less common side effects include altered mental status (5%) and urinary tract infection (UTI; 5%) [13•]. Although rare, serious side effects to the central nervous system may result from elevated serum aluminum levels. Hence, decreased renal clearance is a contraindication to aluminum therapy. When using alum, labs that should be monitored include hemoglobin and hematocrit and serum chemistry profile including creatinine clearance, coagulation profile, and serum aluminum levels.

Westerman et al. performed a retrospective analysis on 40 patients treated with 1% intravesical instillation of alum who had failed prior treatment with CBI and/or cystoscopy with clot evacuation and fulguration [13•]. The patients were treated at a continuous rate of 250–300 cc/h for a median duration of 2 days [13•]. Sixty percent of patients treated required no additional therapy other than CBI prior to hospital discharge [13•]. Moreover, treated patients had significantly reduced 30-day transfusion requirements. Additionally, they found 33% of patients treated with alum required no further treatments for hemorrhagic cystitis at a median follow-up of 17 months.

Aminocaproic Acid (Amicar)

Singh et al. performed a study of intravesical epsilon aminocaproic acid (EACA) in 37 patients with intractable bladder hemorrhage as a result of radiation cystitis or cyclophosphamide [15•]. They treated patients with 200 mg of EACA in 1 L 0.9% sodium chloride solution that was used as a CBI irrigant [15•]. The CBI was continued for 24 h after the urine became clear [15•]. The proposed mechanism of

Table 2 NCI grading system for hematuria

Grade 1	Microscopic hematuria
Grade 2	Macroscopic hematuria
Grade 3	Hematuria with clots warranting hospital admission, blood transfusions, or hemostasis
Grade 4	Hematuria warranting emergency hemostasis
Grade 5	Death

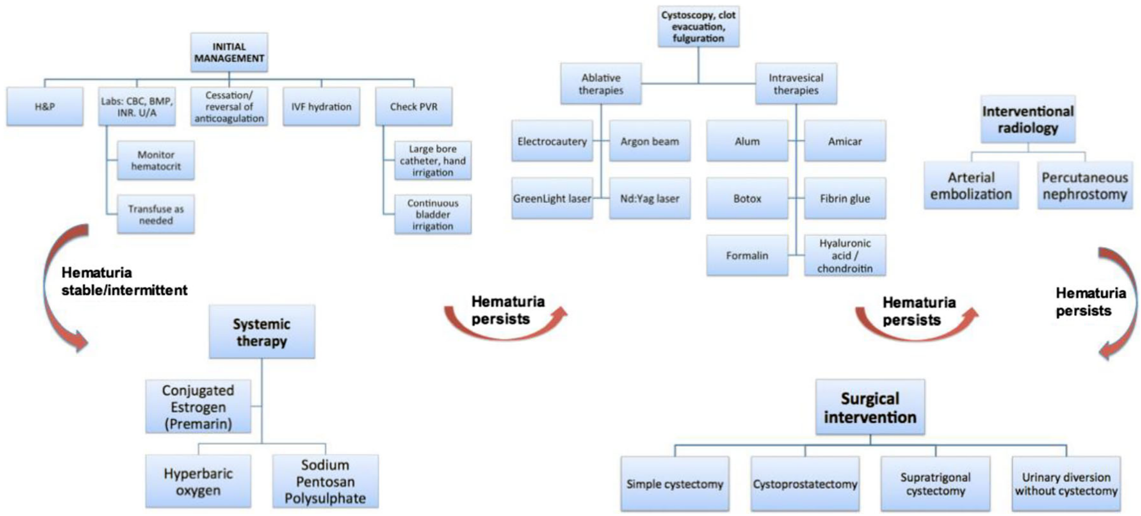

Fig. 1 Acute inpatient management of hematuria

action is an antifibrinolytic activity which counteracts urokinase in the urine [15•]. Among the 14 patients with radiation cystitis, 13 responded to therapy with cessation of bleeding in the acute setting [15•]. Long-term follow-up data were not available in this study.

Botulinum Toxin A

Botulinum toxin blocks acetylcholine release at presynaptic nerve terminals resulting in decreased muscle contractility. Recent research also suggests that botulinum toxin may have anti-inflammatory effects via suppression of COX-2 [16]. Chuang et al. performed a retrospective analysis of botulinum toxin A in 6 patients with refractory radiation cystitis [17]. They injected a total of 200 units at 20 different submucosal sites in the posterior and lateral bladder walls [17]. They noted moderate to significant improvement over a 6-month period in 5 of 6 patients, with mean increase in bladder capacity from 105 to 250 cc and mean decrease in urinary frequency from 14 to 11 episodes per day [17]. No side effects were reported [17].

Fibrin Glue

Fibrin glue is produced from the conversion of the patient's own derived fibrinogen into fibrin I polymer, which activates the final steps of the coagulation cascade upon endoscopic administration [18•]. Bove et al. performed a prospective cohort study on 20 patients treated with a single endoscopic administration of fibrin glue who failed conventional therapy and prior endoscopic clot evacuation and fulguration attempts [18•]. A total of 12 cc of patient-derived fibrin glue was applied in each case. Sixteen patients (80%) had a complete response defined as resolution of LUTS and hematuria, and 4 patients (20%) had a partial response defined as resolution of LUTS but persistent microscopic hematuria. There were no major adverse events, and bladder spasms were the only observed side effect in 6 patients (30%).

Formalin

Formalin causes the precipitation of cellular proteins in the epithelium and the occlusion of small capillaries, which has a fixative effect on friable tissue. Vesicoureteral reflux must be ruled out before its intravesical instillation to avoid ureteral and renal injury. Historically, intravesical formalin was used for refractory cases of hematuria. Typically, a 1–4% formalin solution is used with a dwell time of 10–15 min [19]. Rates of hematuria resolution in the literature range between 70 and 89% [1]. However, formalin instillation is associated with serious complications in up to 30% of patients including bilateral hydronephrosis, anuria, fistula formation, and sepsis/death [1]. For this reason, its use has largely fallen out of favor.

Hyaluronic Acid and Chondroitin Sulfate

Hyaluronic acid (HA) and chondroitin sulfate (CS) are key components within the GAG extracellular matrix layer of the urothelium. They contribute to cell proliferation and migration, and provide a protective barrier against urinary irritants [20••]. They have also been proposed to have anti-inflammatory properties [20••]. Specifically, it has been postulated that they inhibit mast cell degranulation and neutrophil recruitment to the suburothelial space [3, 21].

In a prospective observational study, Gacci et al. identified 30 patients who developed LUTS 3 months following radiation therapy for prostate cancer and treated them with intravesical HA-CS weekly for the first month, followed by additional instillations at weeks 6, 8, and 12 [3]. Using a transurethral Foley catheter, 1.6% HA and 2% CS solutions were instilled into the bladder for a minimum of 1 h [3]. Using the Interstitial Cystitis Symptom Index and Problem Index (ICSI/ICPI) questionnaires, they found that intravesical HA-CS therapy significantly improved overall LUTS and bother scores to baseline values [3]. Specifically, they saw complete recovery in symptoms of urinary urgency, urinary frequency, and nocturia [3]. The main limitation of this study is that placebo arms were not included to differentiate spontaneous recovery of bladder function versus treatment benefit.

Shao et al. performed a randomized study comparing intravesical HA instillations and HBOT in 36 patients with a history of RIHC [20••]. For the HA group, they received weekly instillations of 40 mg of HA for the first month, followed by monthly instillations for the next 2 months [20••]. For the HBOT group, they underwent daily 60 min sessions 7 days per week for a minimum of 1 month with a goal of 30 treatments [20••]. In the HA group, they found statistically significant reductions in urinary frequency and pelvic pain at 12 and 18 months after treatment, respectively. In the HBOT group, they only found a statistically significant reduction in urinary frequency at 6 months following treatment, but similar improvement in pelvic pain. The most common side effect associated with HA instillations was UTI development secondary to repeated catheterizations during the first 6 months of treatment (43% of patients, compared to 10% in HBOT group, $p = 0.034$). Given the significantly lower cost of HA compared to HBOT therapy, studies such as these are important to elucidate the most cost-effective treatment options for hemorrhagic cystitis.

Ablative Therapies

Electrocauterization

Electrocauterization is typically the first-line ablative therapy that is used when a patient with hemorrhagic cystitis is taken to the operating room. Monopolar or bipolar currents may be used depending upon the clinical scenario. In situations with bleeding telangiectasias, as seen in radiation cystitis, monopolar cautery can be used to diffusely coagulate any bleeding surfaces. It should be noted that the choice of irrigant used depends upon the mode of cautery. For bipolar currents, normal saline can be used as conduction only takes place between the edges of the bipolar loop.

Argon Beam

Argon beam coagulation was previously shown to be an effective first-line treatment in hemorrhagic radiation proctitis, with success rates between 80 and 100% [22]. It can be used to target bleeding vessels within the bladder using a narrow-diameter upper gastrointestinal endoscope. Argon gas is delivered as a monopolar current in a non-contact fashion. It has a relatively superficial effect, with a coagulation depth of only 2–3 mm [22].

GreenLight® Potassium-Titanyl-Phosphate Laser Photovaporization

The American Medical Systems® (AMS) GreenLight® laser ablates blood vessels by selectively targeting hemoglobin and sparing surrounding tissue. With the use of potassium-titanyl-phosphate (KTP) crystals, the laser wavelength is reduced from 1064 to 532 nm which discriminates between water and hemoglobin molecules resulting in more efficient tissue vaporization [23, 24••]. The KTP laser has a recommended distance of 3–5 mm from the bladder mucosa which minimizes additional trauma and necrosis [25]. The most recent version is the GreenLight® XPS with TruCoag® laser, which targets erythrocytes with a minimal depth of penetration of 0.8 mm and a coagulation depth of 1–2 mm [23, 25].

Martinez et al. performed a retrospective analysis of 4 patients in whom the GreenLight® XPS laser was used to successfully treat refractory RIHC [23]. They used a setting of 40 watts with a tissue distance of 3–4 mm. All 4 patients had complete resolution of their hematuria, with no further readmissions for hematuria within a 12-month window.

Talab et al. performed a retrospective analysis on 20 patients with RIHC who underwent KTP laser ablation [24••]. They used a 600-μm laser fiber (AMS® Aura GreenLight® laser) with a pulse duration of 10–40 ms, 2 pulses per second, at 10–40 watts of energy. The average laser energy used per procedure was 2171 J (range 130–9879 J). After treatment, patients experienced an average hematuria-free interval of 11.8 months (mean follow-up, 12.6 months), with 65% of patients having complete resolution of their hematuria after only 1 session [24••].

Zhu et al. performed a retrospective analysis of 10 patients who underwent GreenLight® KTP laser ablation of refractory RIHC [25]. They used a side-firing laser fiber with a pulse duration of 40 ms and 20–30 watts of power [25]. They used a mean laser time of 10 min and mean energy of 16.38 kJ [25]. Ninety percent of patients achieved complete resolution with no further treatment over a mean follow-up of 17 months [25].

Nd:YAG Laser

In contrast to the GreenLight® KTP laser, the neodymium-doped yttrium aluminum garnet (Nd:Yag) laser causes non-selective thermal ablation of the mucosa and has a greater coagulation depth of 4–6 mm [22]. Its use in the management of radiation cystitis was first described by Ravi et al. in 1994 [26]. Its effect on the bladder is similar to electric cautery, with increased risk of fibrosis, bladder perforation, and development of a contracted bladder.

Systemic Therapies

Aminocaproic Acid (Amicar)

In addition to being used as an intravesical agent, amicar historically has also been used as an oral agent. Stefanini et al. published a case series using oral amicar (150 mg/kg/day) in 9 patients with macroscopic hematuria for up to 21 consecutive days with effective control of hematuria in all patients [27]. It was well tolerated without any overt adverse events. However, due to concerns over possible systemic side effects, namely hepatic injury, renal impairment, increased risk of thrombosis (DVT/PE), and muscular damage, its use has fallen out of favor in recent years.

Conjugated Estrogen (Premarin)

Conjugated estrogens have been suggested to have beneficial effects in hemorrhagic cystitis via the stabilization of friable blood vessels and capillaries [28]. Liu et al. used it in five patients with refractory hemorrhagic cystitis and obtained an 80% complete resolution rate over a 22-month follow-up period [28]. In two of the patients, the estrogen was administered as an intravenous loading dose twice per day (1 mg/kg) for 3 days, followed by an oral dose of 5 mg daily. These two patients responded with hematuria resolution within the first 8 h of IV therapy. In the other three patients, they received 5 mg oral dose daily with resolution of hematuria within 4–7 days. The main theoretical risks of treatment include thrombosis and hepatotoxicity, although these side effects were not observed in this study [28]. Additionally, long-term use of estrogen poses an increased risk of gynecological cancer.

Mousavi et al. performed a randomized study evaluating the effect of oral conjugated estrogen in 56 hematopoietic stem cell transplant (HSCT) patients with hemorrhagic cystitis [29•]. Patients were randomly assigned to treatment group (6.25 mg daily as an oral dose) vs. control (no therapy). The average duration of therapy was 14 days. They found no benefit in the use of conjugated estrogen with a follow-up period of 100 days. It should be emphasized that the results from this study may not be generalizable, as this is not the typical patient population. Furthermore, they may have used an insufficient dose, as prior studies used either IV estrogen or a higher oral dose.

Ordemann et al. performed a study assessing the use of conjugated estrogen in 10 HSCT patients with a response rate of 70% [30•]. Patients received a starting dose of 6 mg daily in three divided doses, with dose escalation to 12 mg until an improvement in symptoms was seen for a median treatment duration of 5.5 weeks.

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) is the most effective systemic therapy option for radiation cystitis (with or without hematuria), and has the most robust and consistent data in the literature. It involves the administration of oxygen at a pressure greater than atmospheric pressure to increase plasma oxygenation [31]. The resulting increased oxygen delivery to tissue stimulates angiogenesis and tissue regeneration and reduces fibrosis [32••]. HBOT typically involves 90-min sessions for 5–7 days per week over an 8-week period. The mean atmospheric pressure varies by study, with ranges between 1.8–3 atm and a median of 2.4 atm [33••]. The majority of studies are performed with a session time of 90 min, although the range is 60–95 min [33••]. The number of treatment sessions ranges between 20 and 62 with a median of 30 [33••]. Success rates (demonstrating improvement in lower urinary tract symptoms (LUTS) and/or cystoscopic appearance) are quoted between 76 and 95% in the short term and 72–83% in the long term [1]. Rates of hematuria resolution are more variable at 57–92% [1]. Complications include barotraumatic otitis (13%), transient visual disturbances (7%), and paresthesias (1.4%) [31]. The average cost of undergoing at least 30 or more hyperbaric oxygen sessions is approximately $20,000 USD [33••].

Mougin et al. performed a retrospective study on 71 patients who received HBOT for RIHC [31]. They obtained complete and partial response rates of 52.1% and 12.7%, respectively, with a median number of sessions of 29 and median follow-up of 15 months. The average length of time between hematuria onset and HBOT was 8 months. At 1 year, they reported a hematuria-free rate of 70%.

Ribeiro et al. performed a retrospective analysis on 176 patients with refractory RIHC treated with HBOT [34]. They found complete and partial resolution rates of 67% and 22.7%, respectively. The mean follow-up was 12 months, with 15.2% of patients having recurrence during this period. They found that patients with a previous transfusion requirement were significantly less likely to have resolution of their hematuria with HBOT, consistent with other studies demonstrating that earlier intervention is associated with more promising results.

Liss et al. conducted a retrospective review of 22 patients with a history of prostate cancer and RIHC treated with HBOT [35]. Importantly, 91% of patients in this study had severe hematuria (RTOG $\geq$ 3). Forty-four percent of patients had complete resolution of their hematuria after the first 30-session treatment regimen, and an additional 14% of patients had resolution after a second course of HBOT (median follow-up = 2.2 years). The most notable finding in this study was that the severity of hematuria predicted the response to treatment. Patients with more severe hematuria (RTOG 4) were significantly less likely to experience resolution of their hematuria with HBOT compared to patients with less severe forms (RTOG $\leq$ 3). They also evaluated PSA values and found no significant increase as a result of

HBOT. This is noteworthy, as some have raised theoretical concerns regarding the effect of oxygen delivery on tumor regrowth.

Dellis et al. performed a prospective study of HBOT in 38 patients with biopsy-proven severe radiation-induced hemorrhagic cystitis (RIHC) [32••]. They obtained complete and partial response rates of 86.8% and 13.2%, respectively, with a median number of sessions of 33 and a mean follow-up of 29.33 months [32••]. All patients who demonstrated a complete response were treated within 6 months of hematuria onset. A major strength of this study is that it excluded patients who received any prior treatment for their RIHC other than urethral catheterization, bladder irrigation, and/or blood transfusions.

Oscarsson et al. performed a prospective cohort study of HBOT for radiation cystitis [36]. They obtained partial and complete resolution rates of 76% and 31%, respectively, over a 12-month follow-up period [36]. However, they excluded patients with severe hematuria requiring blood transfusions, and so the efficacy may be overstated since only patients with milder forms of the disease were included.

Cardinal et al. performed a meta-analysis on the effectiveness of HBOT for RIHC [33••]. They included 602 patients, and found 84% had partial or complete resolution and 14% experienced recurrence with a median time to recurrence of 10 months [33••]. Factors that predicted treatment success included younger patient age, lower total radiation dose, lower grade hematuria, HBOT initiated within 6 months of symptom onset, and a greater number of HBOT sessions [33••].

Sodium Pentosan Polysulfate

Sodium pentosan polysulfate (SPP) is a synthetic polysaccharide that is believed to replenish GAGs in the urothelium thereby reducing urothelial permeability [37]. SPP is also thought to have anti-inflammatory properties including inhibition of mast cells and decreased release of NF-κB [37]. Hampson et al. evaluated the use of sodium pentosan polysulfate (SPP), administered in sublingual form at a dose of 100 mg TID, in 14 patients with hemorrhagic cystitis due to either radiation or cyclophosphamide with complete resolution of hematuria in 21% of patients [38]. Sandhu et al. reported the use of SPP in 51 patients with either radiation or cyclophosphamide-induced hemorrhagic cystitis [37]. They found a complete and sustained cessation of hematuria in 20% of all patients with a median follow-up of 450 days [37].

Interventional Radiology

Arterial Embolization

For severe intractable hematuria unresponsive to conservative measures, some have advocated for either arterial embolization or surgery. Arterial embolization is an attractive option, especially in patients who are poor surgical candidates as it is associated with lower rates of morbidity and mortality. Historically, non-selective embolization of the internal iliac arteries has been described in cases of intractable bleeding; however, with modern advancements in Interventional Radiology, more selective embolization is now feasible.

Mohan et al. performed a retrospective review of 9 patients who underwent superselective vesical artery embolization using polyvinyl alcohol (PVA) particles for intractable bladder hemorrhage [8•]. Specifically, they embolized the largest vesical artery arising from the anterior trunk of the internal iliac artery bilaterally. They achieved complete resolution of hematuria within 48 h in all patients. One patient experienced post-embolization syndrome that improved with conservative measures. Three patients experienced mild transient post-embolization gluteal and/or thigh pain. There were no other significant complications. Over a mean follow-up of 14.45 months, 1 patient experienced mild recurrent but self-limited hematuria. While long-term complications from arterial embolization of the bladder are rare, there have been case reports of bladder necrosis occurring within 2–4 weeks post-embolization (39–43). Factors that may contribute in the development of this devastating, life-threatening complication include tissue hypoperfusion, bilateral embolization, and less selective internal iliac artery embolization (39). There is an increased risk of tissue hypoperfusion in patients without good collateral blood flow (i.e., due to underlying vasculopathy) or in situations of systemic hypoperfusion such as sepsis or hypovolemia (39). It has also been suggested that the size of the microspheres used for embolization may play a role in the development of this complication, with smaller particle sizes (< 500 μm) carrying an increased risk (39). Hence, care should be taken to match the size of the embolic agent with the target vessel (39).

Percutaneous Nephrostomy

Several case reports have been published demonstrating that percutaneous nephrostomy tubes are a safe and effective method at controlling bleeding in refractory cases [9, 10]. In theory, the diversion of urine away from the bladder should decrease bleeding as it eliminates the lytic effect of urokinase on clots and therefore facilitates hemostasis [44••]. With supravesical urinary diversions in which the bladder is left in situ, 80% of patients continue to experience complications and 35% will ultimately require cystectomy [44••].

Surgical Intervention

Definitive surgical management may be considered in cases of intractable hemorrhage. Linder et al. retrospectively reviewed 21 cases of hemorrhagic cystitis treated with cystectomy between 2000 and 2012 [44••]. Ninety-five percent of the patients in this study had a history of pelvic radiation. Regarding surgical technique, 57% of patients underwent a simple cystectomy and 43% underwent a cystoprostatectomy. Of the patients in the simple cystectomy group, 33% underwent a supratrigonal cystectomy in an effort to avoid rectal injury, as there was significant fibrosis between the bladder and rectum posteriorly. Eighty-six percent of patients received an ileal conduit, 4.8% received a colon conduit, and 9.5% received bilateral ureteral ligation necessitating nephrostomy tube dependency. The median postoperative length of stay was 10 days, and 42% of patients experienced severe (Clavien grade III or higher) complications. The 90-day all-cause mortality rate was 16%, and 1-year and 3-year overall survival rates were 84% and 52%, respectively. Due to the high perioperative morbidity and mortality associated with cystectomy, this option should serve only as a measure of last resort.

Future Directions

Angiogenesis Therapy

Soler et al. demonstrated that angiogenesis therapy may be useful in preventing the underlying pathogenesis of radiation cystitis [45]. In their study, 30 rats were radiated with a single dose of 20 Gy. One month following radiation, the animals were divided into four groups: (1) healthy control group (non-radiated rats), (2) treatment-control—PBS group, (3) vascular endothelial growth factor (VEGF) group, (4) endothelial cells (EC) group. Injection solutions were prepared (final volume = 50 uL), with added collagen to help keep the cells at the injected site within the bladder. Intravesical injections were then given as a single dose, and tissue was analyzed at 1.5 and 3 months post-radiation. Results demonstrated that the use of EC and VEGF promoted neovascularization and inhibited collagen deposition within the bladder wall of irradiated rats [45].

Intravesical Liposomal Tacrolimus

Tacrolimus is a potent immunosuppressant and inhibitor of calcineurin, which decreases the production and release of pro-inflammatory cytokines within T cells [46]. It has previously been shown to have beneficial effects on inflammatory skin conditions when applied topically without any systemic side effects [47]. Due to its hydrophobic properties, drug delivery across mucosal surfaces is limited. Hence, using hydrophilic substances such as liposomes enhances drug delivery and mucosal solubility [46]. Systemic administration can be associated with side effects which are dose-dependent, most commonly nephrotoxicity and hypertension through vasoconstriction [48].

Raja et al. developed a rat model of radiation cystitis in which 21 rats were irradiated with a single dose of 40 Gy using an image-guided small animal irradiator (SARRP) which aims to model the method of radiation delivery used in humans [46]. Of these rats, 12 received intravesical liposomal tacrolimus and 9 received intravesical saline. The liposomal tacrolimus group demonstrated significantly improvement in urinary frequency to baseline levels ($p = 0.019$). In a rat model of cyclophosphamide-induced inflammatory cystitis, Chuang et al. found that rats treated with liposomal tacrolimus had a significantly reduced inflammatory response and decreased bladder overactivity through the modulation of IL2, PGE2, and EP4 [47]. Furthermore, systemic levels of tacrolimus remained below the detection limit of the most widely used clinical assay (< 1.5 ng/mL).

Dave et al. published a clinical case report in 2015 in which an 81-year-old male with refractory severe RIHC was treated with a 30-min bladder instillation of intravesical tacrolimus (0.125 mg/mL) on two consecutive days [48]. The treatment was well-tolerated, the serum tacrolimus level remained below the normal reference range, and complete resolution of hematuria was achieved.

Interstitial Cells

Interstitial cells (ICs) are located in the lamina propria and are thought to regulate afferent neuronal control of the urinary bladder. ICs have been implicated in the pathophysiology of conditions such as diabetic bladder dysfunction, overactive bladder, and neurogenic bladder after spinal cord injury [49]. They are characterized by their expression of c-kit. In a rat model, Giglio et al. found that bladder radiation caused decreased efferent neuronal signaling leading to weaker contractions, but increased firing of afferent nerves [49]. In vivo electrical field stimulation (EFS) of pelvic nerve afferents caused increased bladder contractions in irradiated bladders compared to non-irradiated bladders, which suggests that radiation sensitizes the micturition reflex [49]. Additionally, the use of imatinib, a c-kit inhibitor, inhibited bladder contractions (both EFS and stretch-induced) in controls but not in irradiated bladders [49]. This suggests that ICs may play a role in regulating the micturition reflex and are negatively affected by radiation therapy leading to increased afferent nerve sensitivity [49].

Genetic Predisposition

Osti et al. performed a retrospective study in which they analyzed single nucleotide polymorphisms (SNPs) of DNA repair genes in 67 patients with locally advanced rectal cancer who were treated with neoadjuvant chemoradiation [50]. They found significantly higher rates of grade ≥ 3 urinary frequency/urgency in patients who were homozygous (AA) or heterozygous (Aa) for the XRCC3 gene SNP compared to wild type [34]. XRCC3 encodes for a protein that dimerizes with the RAD51 protein and is involved in the DNA repair process during homologous recombination [50]. Mutations in this enzyme lead to increased rates of chromosomal aberrations [50]. This suggests the potential importance of genetic polymorphism screening to identify patients at risk for developing complications and to guide more personalized treatment regimens.

Conclusion

Radiation cystitis is a devastating disease process that can occur months to years following radiotherapy. It poses many therapeutic challenges, especially when associated with ongoing blood loss anemia. There are a myriad of treatment options, including intravesical instillations, ablative procedures, systemic therapies, hyperbaric oxygen therapy, arterial embolization, and urinary diversion. Hyperbaric oxygen therapy has emerged as an outpatient treatment option with very promising results; however, further research needs to evaluate its long-term cost-effectiveness. Various intravesical treatment options appear effective at mitigating radiation-induced lower urinary tract symptoms, and are significantly less costly than hyperbaric oxygen. When conservative measures fail to control bladder hemorrhage, arterial embolization or urinary diversion may be ultimately necessary as life-saving measures. Cystectomy with urinary diversion is associated with considerable morbidity and mortality, and should serve only as a measure of last resort. Due to the devastating impact of radiation cystitis on patient quality of life, further research is imperative in order to add further innovative treatment strategies to the urologist's armamentarium.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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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