Clinical management of radiation cystitis: a narrative review

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Abstract: Radiation therapy for various pelvic cancers has led to secondary complications becoming increasingly commonplace. Radiation cystitis is an undesired side effect with a wide spectrum of severity ranging from mild irritative voiding symptoms to life threatening hemorrhagic cystitis (HC). As such, the management of radiation cystitis too has a wide range of potential treatment options. Hyperbaric oxygen therapy can be utilized in the outpatient setting in the stable patient. For the more symptomatic patient, emptying the bladder of any clots followed by continuous bladder irrigation is first line treatment. If the bleeding persists after this, systemic therapies such as systemic tranexamic acid (TXA) or sodium pentosan polysulfate (Elmiron®) are options however these have mixed outcomes in the literature. Intravesical treatments of aminocaproic acid (Amicar), aluminum or formalin can be trialed to abate bleeding, however each come with their own side effect profiles. In the case of refractory bleeding to these conservative measures, or in the unstable patient, vascular embolization can be utilized. Urinary diversion with or without cystectomy is a definitive treatment however these surgeries are generally more complicated due to the radiation history. Herein, we review in detail the relevant literature of available medical and surgical techniques for treatment as well as offer our own experience in managing this challenging disease process.

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Introduction

With an estimated 16.9 million Americans living with a history of cancer, cancer survivorship is an important and growing issue (1). Use of ostensibly less invasive radiation treatment modalities to treat pelvic cancers is also increasing as are their resulting adverse effects (2-5). Radiation cystitis is a well described complication of pelvic radiotherapy that can lead to very bothersome lower urinary tract symptoms, a contracted poorly compliant bladder as well as very difficult to manage hematuria. Complications of radiotherapy account for as many as 7% of emergent urologic admissions to the hospital that most commonly manifest as hemorrhagic cystitis (HC) (6). In this review, we will discuss the common medical and surgical interventions used to manage radiation cystitis, with a particular focus on HC.

While some formalized algorithmic guidelines do exist (7), acute complications of radiation cystitis generally result from hemorrhage and are thus based on hemodynamic stability and clinical acuity of the patient (8). In the acute setting, adequate fluid resuscitation as well as evacuating the bladder of potential clots is of seminal importance and needs to be accomplished quickly. Bladder evacuation can be accomplished by either a large bore catheter with subsequent continuous bladder irrigation or with a cystoscope under general anesthesia with fulguration

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of bleeding areas as needed. Also, on initial presentation of radiation induced cystitis, recurrent or secondary malignancy must be ruled out with tissue sampling.

Depending on the severity, timing and chronicity of the patient's symptoms, various treatment strategies exist ranging from systemic medications to intravesical therapies to more invasive surgical options. Herein we will describe the various treatment options available as well as their efficacy in modern series. Hyperbaric oxygen has been thoroughly described to be a non-invasive, effective and well tolerated treatment option will not be discussed in this review. We present the following article in accordance with the Narrative Review reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-20-169/rc).

Systemic therapies

Sodium pentosan polysulfate (SPP)—marketed as Elmiron® (Janssen Pharmaceutica, Beerse, Belgium)—is postulated to replete the deficient protective glycosaminoglycan (GAG) layer of the bladder which is primarily used for treatment of interstitial cystitis (9). However, there are studies showing improvement of those with HC. In one such series of 51 patients receiving 100 mg oral SPP three times daily for treatment of their HC, 21 had improvement in their symptoms—10 of which had complete resolution of symptoms (10).

More commonly used systemic agents are those acting on the fibrinolytic pathway. Tranexamic acid (TXA) functions by enzymatic inhibition of fibrinolysis and has been use to alleviate bleeding in the critical care arena for many decades (11). Studies investigating its utility in urology have had mixed results, leaning towards showing no clinical benefit (12-14). A randomized, double-blind, placebo controlled trial in 2017 of 131 patients undergoing transurethral resection of the prostate and transurethral resection of bladder tumor received either intravenous TXA or intravenous saline in the peri- and post-operative periods. The results showed no difference in intraoperative blood loss or postoperative transfusion requirements (14).

Intravesical therapies

Aminocaproic acid (Amicar) is a lysine analogue and acts as an enzymatic inhibitor to prevent fibrinolysis, thereby stabilizing endogenous clotting mechanisms. It was initially implemented in critical care settings in the 1950's for management of patients with systemic coagulopathies and remains in use today. The most recent report in the urologic literature however is from 1992 wherein 34 out of 37 patients clinically responded to intravesical instillations (15). Intravesical Amicar is still anecdotally used in clinical practice despite its sparse evidence of utility.

Intravesical aluminum salts (alum) act as astringents, leading to protein precipitation with decreasing capillary permeability and vasoconstriction. The mechanism of action and its intravesical use for controlling HC in six patients was first described by Ostroff and Chenault in 1982 (16). It is prepared as a 1% solution (5 g alum dissolved in 5L sterile water) and the bladder is irrigated continuously at a rate of 250–300 mL/hour (17). There is no need for the patient to undergo anesthesia to undergo this treatment. A 2016 study in Brazil (18) used intravesical alum on 40 patients with intractable HC who failed initial continuous bladder irrigation with normal saline; 24 patients (60%) required no further treatment beyond the intravesical alum during that admission and 13 patients (32.5%) required no further treatment at a median follow up of 17 months. While there are case reports of aluminum toxicity via systemic absorption in patients with renal dysfunction (19,20), it is generally well-tolerated with few-to no patients in the Brazilian series had adverse systemic reactions.

The use of intravesical formalin for refractory hematuria was initially reported on in 1973 for severe hematuria with a success rate of 90% (21). These promising results came with very severe side effects of contracted, painful and non-compliant bladder at the used concentration of 10%. This treatment must be completed under anesthesia since its mechanism is of a tissue fixative and can cause significant pain to the patient. Since initial reports, we have learned that starting at a lower concentration of 1% for 10 minutes can achieve equally successful outcomes while limiting side effects (17). Due to the caustic nature of formalin, a cystogram must be performed prior to instillation to rule out vesicoureteral reflux to avoid ureteral damage. If reflux is found on cystogram, ureteral occlusion balloons may be used to protect ureters during formalin instillation. Most studies report positive results ranging from 71–89% clinical response rates (22-25). Current recommendations are to instill intravesical 1–2% formalin for 10 minutes under spinal or general anesthesia with a bladder emptied of all clots after evaluating for vesicoureteral reflux (7).

Surgical therapies

If conservative measures fail to resolve the hematuria from

HC, then more invasive and permanent options such as vascular embolization or urinary diversion may be required. Urinary diversion in the form of bilateral nephrostomy tubes is a commonly used therapy, however, there is very little data supporting the course. It is described in a small series that showed resolution of hematuria in 3 of 6 patients (26). This line of therapy may be used at any point in the treatment process.

In acute settings, the patient's hemodynamic status and ability to clinically stabilize can dictate the progression of these interventions. Arterial embolization is an option both in the unstable patient with acute hemorrhage as well as the refractory bleeding patient as it will theoretically offer an immediate cessation of blood loss. Results are quite mixed however due to the variability of patients receiving this intervention. Some reported cohorts of 10–20 patients show that embolization of the superior vesicle artery results in 81–100% resolution of hematuria, with minimal side effects and mean follow up greater than 1 year (27,28). Other studies show outcomes of cessation of bleeding at rates of 80–90%, however they also report on mortality rates of 20–66% (29,30). Embolization clearly has a place in the acute setting for an unstable patient with refractory bleeding, however, given the disparity of reports, and lack of long term follow up, embolization should be approached cautiously in the stable patient.

The most definitive option to resolve HC is permanent urinary diversion. The choice of cystectomy with urinary diversion depends on several factors and has demonstrated mixed results. A 2014 study from the Mayo Clinic reported on their series of 21 patients who underwent cystectomy with urinary diversion for intractable hematuria refractory to less invasive interventions. Outcomes for their cohort showed a 90-day mortality rate of 16%. One- and three-year survival rates of the remaining patients were 84% and 52%, respectively (31).

If a patient suffers from less acute complications of radiation, such as contracted bladder, intermittent hematuria, or devastated outlet, then the patient and their urologist may choose a continent form of diversion. In our series of continent cutaneous ileocecal cystoplasty—the "Hemi-Indiana Pouch"—for devastated bladder outlets, 10 of 13 patients had a history of radiation (32). In that population, 5 of the 10 patients had episodes of recurrent hematuria, which had resolved in all patients after the augmentation. It has been postulated that the intestine has protective effects on chemotherapy induced HC (33). Similar protective effects for radiation induced HC have not been studied. In our initial series, augmentation of the radiated bladder was used to obviate the need for a ureteral anastomosis. However with current technologies using intraoperative indocyanine green to evaluate ureteral perfusion, the rate of ureteroenteric strictures have substantially diminished to the level where we now in fact favor the full Indiana pouch with cystectomy over an augmentation in these patients (34).

Conclusions

Urologic complications of pelvic radiation are increasing in the past decades with HC being a common clinical challenge to manage. Many treatment options exist depending on the severity of the symptoms and should be tailored to the patients presentation and goals. In the acute setting, stabilizing the patient with fluid resuscitation as well as evacuating the bladder of clots is paramount. If this doesn't resolve the hematuria, then more invasive options are required. Multiple intravesical as well as systemic therapies are available and the option of one over the other is not well established and multiple treatment modalities can and should be attempted prior to progressing to a more permanent surgical option. In the unstable patient, vascular embolization is a valuable treatment to stop bleeding relatively quickly. If permanent urinary diversion is required, we prefer a continent cutaneous urinary diversion in the form of an Indiana Pouch with cystectomy.

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