Radiation Colitis and Proctitis

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ABSTRACT

Radiation therapy is commonly utilized as a major component in the treatment of pelvic malignancy. Unfortunately, secondary toxicity to the lower gastrointestinal tract can occur. This most commonly affects the rectum, although injuries to the colon and small intestine are not uncommon. The presentation can be acute or chronic, and different mechanisms are responsible for each. Symptomatology is quite variable but can result in significant compromise for the patient. Numerous preventive and treatment strategies have been applied to this disease process. This article presents a summary of the current knowledge regarding radiation injury to the lower gastrointestinal tract with special emphasis on treatment options for radiation proctitis.

KEYWORDS: Radiation, radiotherapy, colitis, proctitis, enteritis

Objectives: Upon completion of this article, the reader should understand the etiology, manifestations, and treatment of radiation-induced colon and rectal injuries.

Radiation therapy is a major component of the treatment armamentarium for a variety of malignancies. Regardless of the tumor cell types, radiation may play a central, adjuvant, or neoadjuvant role. In the case of many gynecologic, urologic, and rectal cancers, radiation treatment is limited to the pelvis, where a maximum benefit can be delivered to the target tissue while minimizing inadvertent irradiation of other organs. Unfortunately, the radiation fields required to treat these pelvic and sometimes intra-abdominal or retroperitoneal tumors often include the small bowel and colon as well. Over the years, several modifications to radiotherapy have been made to minimize potentially harmful side effects. These have included patient positioning, specialized treatment tables,¹ limited treatment dosage^{2,3} and multiportal delivery techniques.^{3,4}

Despite optimization of delivery, radiation therapy of cancer will continue to be dose limited by normal tissue tolerance. Among the most common and potentially most devastating bystander effects are those affect-

ing the normal bowel. This can include the small intestine, colon, and rectum. Although radiation enteritis is commonly described, the following review concentrates on radiation colitis and especially proctitis. We explore the differences between the acute and chronic process and assess current prevention and treatment strategies.

RADIATION THERAPY

Emil Herman Grubbé was the first to use radiation clinically to treat cancer. In 1896 he treated a patient with an advanced, locally recurrent breast cancer with 18 daily 1-hour exposures.⁵ The condition was relieved but unfortunately the patient succumbed to metastatic disease. As our understanding of both radiation and the biology of cancer has increased, utilization of radiation therapy has become much more proficient. Imaging devices, such as computed tomography (CT) and magnetic resonance imaging, have enabled the radiation

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oncologist to perform three-dimensional planning and conformal dosimetry to deliver external beam radiotherapy. Brachytherapy with radium beads has become more popular, and intraoperative therapy continues to be an active area of investigation. In addition, chemotherapeutics that seem to serve as “radiosensitizers” are now being utilized in the treatment of many cancers.^{6,7}

Despite these major advances in the field of radiation oncology, radiation enteropathy continues to be a major obstacle to the radiocurability of abdominal and pelvic tumors. The incidence of bowel-related toxicity after radiotherapy treatment is quite variable. Much of this variability is dependent on treatment dosing schedules, which vary with cancer type. For example, the typical external beam radiotherapy (EBRT) treatment regimen for rectal adenocarcinoma totals 50 Gy over a 5-week period in the United States or 25 Gy over 5 days in Europe. This contrasts with the treatment for prostate carcinoma, which typically receives 75 Gy over 7 to 8 weeks, or cervical carcinoma, which might receive 45 Gy EBRT plus a variable dosing of brachytherapy. It is also difficult to discern the degree of inadvertent dosing received by the normal bowel, although it would be expected to be quite variable. The reported incidence of bowel toxicity during treatment of prostate cancer ranges from 3% to 19%.^{8,9} Similarly, an estimate of the likelihood of developing radiation-induced bowel injury during treatment of rectal adenocarcinoma in the adjuvant setting is 19% at 5 years.¹⁰ Unfortunately, bowel toxicity cannot be predicted and assessment by a variety of toxicity grading scales adds further difficulty in defining the actual incidence of radiation-related toxicity.

TOXICITY GRADING SYSTEMS

Numerous grading systems are utilized in the literature to assess bowel toxicity from radiotherapy. Currently, the most commonly utilized systems for acute and chronic bowel toxicity are those proposed by the Radiation Therapy Oncology Group (RTOG) and the European Oncology Radiation Therapy Group (EORTG).¹¹ Although these scales allow a standardized assessment based on patients' symptoms, it does not take endoscopic, histologic or subject continence into consideration. The RTOG criteria assess acute morbidity (day 1 through day 90), and the RTOG/EORTC criteria assess late radiation effects. Another assessment of the chronic effects of radiotherapy is often made by the Late Effects on Normal Tissues (LENT) Subjective, Objective, Management and Analytic (SOMA) grading system.¹² Finally, the National Cancer Institute has evolved the Common Terminology Criteria for Adverse Events (CTCAE) v.3.0, formerly Common Toxicity Criteria (CTC), to represent a more global assessment of cancer treatment-related toxicity.¹³ Most recently, both the

LENT-SOMA and RTOG scores have been correlated with a combination of the inflammatory bowel disease (IBDQ) and Vaizey incontinence questionnaires.^{14,15} The authors argue that these self-questionnaires offer a broad and more sensitive measure of gastrointestinal (GI) toxicity after radiotherapy in both the acute and chronic phases.¹⁴ However, it is unknown whether this increased sensitivity is clinically relevant.

ACUTE RADIATION INJURY

Acute intestinal injury induced by ionizing radiation is directly related to the dose and frequency at which radiation is given. The effects of ionizing radiation on the intestinal mucosa in the acute setting are generally ascribed to inhibition of epithelial cell mitosis deep within the mucosal crypts.¹⁶ However, radiation does not inhibit cell migration up and out of the crypts onto the villi. This loss of mitotic activity coupled with continued cell migration leads to denudation of the mucosal surface. Loss of mucosal surface leads not only to loss of water, protein, and electrolytes but also to loss of the mucosal protective barrier. Therefore, the gut is rendered permeable to bacteria and other antigens, which may exacerbate the inflammatory response and perhaps lead to bacteremia. In addition to its effects on the mucosa, radiation affects bowel motility. Utilizing a dog model, Otterson and colleagues observed the generation of giant migrating contractions after the first dose of radiation, which continued throughout the treatment period but ultimately returned to normal.^{17,18} The exact mechanism behind these motility changes remains elusive. However, it was apparent that these migratory changes correlated with symptoms of diarrhea and cramping.¹⁷

Overall, it is estimated that up to 50% of patients who undergo abdominal or pelvic radiation develop acute toxic effects of the bowel.¹⁹ Unfortunately, there are no specific treatments for the acute effects of radiation colitis. The more common symptoms of diarrhea, abdominal pain, and tenesmus are usually self-limited and short-lived. Typically, the management of these patients is symptomatic and supportive.

CHRONIC RADIATION INJURY

In contrast to acute radiation injury, chronic injury is an indolent process that can arise 3 months after therapy completion or up to 30 years later. In addition to the acute cellular toxicity, radiation causes a progressive, obliterative arteritis and submucosal fibrosis. Transmural injury of the bowel wall can lead to a progressive vasculitis, thrombosis, and, ultimately, varying degrees of ischemia and necrosis. This process may lead to narrowing of the bowel lumen and eventual obstruction. The effects of chronic radiation are primarily related to

the total dose of radiation received as well as the total volume of tissue irradiated.¹⁹

There is some evidence to suggest that *chronic* radiation proctitis is more likely to occur in those initially experiencing severe *acute* proctitis.^{20,21} This has been termed the consequential late effect.^{22,23} However, the absence of acute complications does not protect against the development of chronic radiation-induced injury. Several other factors have been identified that may increase the likelihood of developing chronic radiation injury. They include a history of prior abdominal or pelvic surgery,²⁴ presumably secondary to adhesion formation resulting in entrapment of the bowel. In an attempt to limit the radiation dose delivered to normal bowel, Green investigated the utility of preradiation contrast radiography to determine the proximity of the bowel to the target organ.²⁵ He found that patients who had prior abdominal or pelvic surgery were more likely to have bowel at risk and this bowel was unable to move from the radiation field. In addition to prior surgery, a history of vascular occlusive disease seems to be a predisposing factor for the development of radiation enteritis.^{26,27} Therefore, patients with underlying hypertension, diabetes, and cardiovascular disease may be especially at risk for the development of symptomatic radiation enteritis.

Late intestinal injury may arise with a variety of signs and symptoms ranging from chronic abdominal pain, constipation, obstruction, or mild GI blood loss to the sudden onset of abdominal pain and toxemia consistent with an acute abdomen. Any patient with a history of radiation to the abdomen or pelvis presenting with GI complaints should raise suspicion for radiation-related toxicity until proved otherwise. One must keep in mind that patients with chronic radiation changes often develop dense intra-abdominal adhesions after radiation exposure and have very little free domain in their abdomen. Localized perforations may occur, and an elevated awareness is required to avoid missing a life-threatening diagnosis. On the other hand, exploratory surgery for chronic radiation injury should be approached with caution, as surgery carries significant morbidity and mortality in this population of patients.^{28,29} In the nonemergent, radiated surgical patient, preoperative imaging is an important component that can be critical in assisting the surgeon in planning the operation.³⁰⁻³² Radiographic assessment of chronic radiation enteritis or colitis has most commonly utilized barium enema or CT. A spectrum of findings has been demonstrated on barium enema, ranging from normal findings (seen in 15%) to ulceration and contour abnormalities, intestinal fixation, decreased distensibility, and stenoses.³³ The "omega sign," caused by bilateral retraction at the base of a narrowed sigmoid loop, was seen in nearly 60% of patients with radiation colitis. Endoscopy was found

to be complementary to barium study as it allowed better assessment of mucosal abnormalities and ulceration.³³ Surprisingly, CT was not found particularly useful in diagnosing radiation enteritis.^{30,31} The findings required correlation with the clinical history and were generally nonspecific, including bowel wall thickening and stenosis.

RADIATION COLITIS

Little has been written about the specific effects of radiation on the colon. However, reports of nonrectal radiation-induced intestinal injury (NRRII) have been published and one can extract from these series some information regarding injury to the colon. It seems that the most likely symptoms occurring in patients with radiation colitis include diarrhea or tenesmus. In addition, patients may present with obstruction or perforation. In one series where patients received postoperative radiation therapy for stage IB or IIA cervical cancer, the incidence of NRRII was 22%.³⁴ Risk factors for developing radiation enteritis included radical hysterectomy, radiation dosages to the lower pelvis exceeding 54 Gy, and age over 60 years.³⁴ These findings have been supported by others who have demonstrated higher rates of intestinal complications in elderly people after definitive radiotherapy.¹⁰ Additional evidence has indicated higher rates of intestinal complications following radiation therapy in patients receiving larger volumes of radiation.^{35,36} Taken together, these data indicate that smaller doses administered to limited fields might result in a decreased incidence of intestinal complications following radiation therapy.

Although it is difficult to assess the exact incidence of radiation-induced colitis, given the susceptibility of normal tissue to ionizing radiation, it is inevitable that a proportion of patients develop this complication. Therefore, investigations into future preventive strategies are important. Maneuvers that minimize small bowel and colon exposure to radiation can be taken during the delivery of radiation. For example, placing the patient in a Trendelenburg (head down) position during pelvic irradiation assists in moving the bowel out of the pelvis. Using multiple fixed or rotational radiation fields also minimizes exposure of any one segment of normal bowel to excessive radiation doses.

Several authors have also investigated preventive surgical techniques to exclude the bowel from the pelvis at the time of planned surgical resection but prior to subsequent radiation. For example, Lechner and Cesnik reported their experience with an omental sling for keeping bowel from entering the pelvis after rectal resection.³⁷ After postoperative radiation therapy, they reported no evidence for subsequent radiation enteritis. Others have reported the use of saline tissue

expanders as well as absorbable mesh to displace the bowel from the pelvis.³⁸ Finally, there has been a tremendous push to develop medications that serve as radioprotectants.³⁸

Aside from preventive strategies, eventual treatment approaches may also be required and are likely to be surgical. Although surgical intervention in the setting of chronic radiation enteritis can be fraught with complications, it is often necessary. Galland and Spencer reported their most recent series in 1986, demonstrating an anastomotic leak rate of 7%, which was significantly less than the 50% leak rate previously reported by this group.^{39,40} In their latest account, the authors reported that the ascending, transverse, and descending colon is rarely involved with radiation injury and whenever possible an anastomosis should be performed utilizing at least one of these uninjured limbs.

RADIATION PROCTITIS

Of all the GI organs, the rectum is most commonly affected by pelvic radiotherapy.⁴¹ It has been estimated that 75% of subjects receiving pelvic radiotherapy experience rectal symptoms during treatment and almost 20% continue with chronic proctitis.⁴² In addition, 5% may develop perirectal fistulas, strictures, or incontinence. Unfortunately, as the rectum is a fixed structure within the pelvis, the usual maneuvers taken to limit radiation-related bowel toxicity may not apply. The symptoms are usually related to loose stools, urgency, bleeding, pain, or tenesmus. Although these acute symptoms have been shown to progress throughout treatment, endoscopic and histologic findings appear to peak after 2 weeks of radiotherapy and may stabilize or regress through completion of treatment.⁴³ Endoscopy in this setting can reveal friability and granularity, pallor, erythema, or prominent submucosal telangiectasias.⁴⁴ In addition, histologic findings in the acute phase classically demonstrate epithelial meganucleosis, fibroblastic proliferation, and absence of mitotic activity. This differs from the chronic findings of severe vascular changes such as telangiectasia of capillaries, platelet thrombus formation, and narrowing of arterioles always accompanied by lamina propria fibrosis and crypt distortion.⁴⁵

Although rectal bleeding is most often the presenting symptom of chronic proctitis in the setting of prior radiation, it should not be assumed that this is the sole cause. In fact, endoscopic findings reveal that one third of diagnoses in this setting were unrelated to the previous radiotherapy and significant neoplasia was noted in 12%.⁴⁶ Because clinical symptoms alone are unreliable for diagnosis, endoscopic evaluation is mandatory with new onset of hematochezia after prior radiation therapy.⁴⁷

TREATMENT APPROACHES

Because the previously described preventive strategies to limit radiation toxicity cannot be applied to the fixed rectum, medical means are often utilized in this regard. Numerous therapeutic agents have been evaluated and/or are currently utilized against radiation-induced proctitis. When considering treatment strategies, two approaches can be taken. First is a *prevention* strategy where the agent is given before and during the radiation treatment and aimed at averting the onset of symptoms before they occur. The second and more common approach is simply *treatment* of the process after the symptoms of radiation proctitis have developed. This may apply to the acute phase or the chronic condition. Both of these approaches, when existent, are considered and incorporated into the following treatment options.

Anti-Inflammatories

In many cases, patients presenting initially with symptoms suggestive of radiation proctitis are first offered treatment with anti-inflammatory medications. This most commonly involves either oral or enema-delivered steroids or various 5-aminosalicylic acid (5-ASA) preparations. Although they are often utilized in both the acute and chronic settings, evidence is lacking for the use of steroid preparations in the treatment of radiation proctitis. One small prospective crossover trial utilizing betamethasone enemas for chronic proctitis failed to show any clinical benefit.⁴⁸ However, if a benefit of steroid treatment does exist, it would seem more likely for the acute rather than chronic process. To date, a handful of prospective, randomized, controlled trials have evaluated the use of 5-ASA compounds in the prevention of acute enteritis or proctitis. Although earlier studies utilizing oral mesalazine and olsalazine failed to demonstrate that these agents are beneficial,^{49,50} more recent trials using oral sulfasalazine and balsalazide have shown promise as preventive agents against proctitis symptoms.^{51,52} This may relate to the enhanced ability of these newer agents to act primarily on the colon and rectum.

It is equally difficult to conclude on the utility of 5-ASA compounds for the treatment of established proctitis. A prospective, randomized trial compared oral sulfasalazine plus rectal steroids with rectal sucralfate and oral placebo. The sulfasalazine regimen did demonstrate a significant improvement in both clinical symptoms and endoscopic findings; however, by comparison, clinically this was less effective than sucralfate.⁵³

Sucralfate

The ability of sucralfate to evoke a protective barrier and promote epithelial healing has allowed its use in the treatment of radiation proctitis. Although the previously

mentioned trial and subsequent follow-up^{53,54} have demonstrated a benefit of sucralfate in the treatment of chronic proctitis, no other high-level evidence exists. The majority of literature involving sucralfate investigates its use as a preventive agent. Several randomized, controlled trials comparing oral or rectal sucralfate with placebo in the prophylaxis of acute proctitis have failed to show benefit in preventing symptoms or improving RTOG/EORTC or CTC grade.⁵⁵⁻⁵⁷ Similarly, these authors did not find a benefit for sucralfate in preventing late proctitis.⁵⁸ However, one randomized, controlled trial found that oral sucralfate decreased diarrhea symptoms in both the acute and chronic phases.⁵⁹

Short-Chain Fatty Acids

Short-chain fatty acid (SCFA) enema preparations have also been evaluated as treatment (rather than preventive) agents for radiation proctitis. Because SCFAs act as a major fuel source for colorectal mucosa, it was hypothesized that their addition might be useful in overcoming some of the toxic effects of radiation therapy. Two small randomized, placebo-controlled trials have examined the use of SCFA enema treatments for chronic proctitis. One of these trials found no benefit for topical butyric acid over a 2-week treatment period, but the other study using a butyrate-containing SCFA solution over a 5-week period noted more rapid improvement in symptoms and endoscopic findings compared with placebo controls.^{60,61} Another small randomized, controlled crossover study again utilizing butyric acid enemas for treatment of acute proctitis noted improvement in symptoms and endoscopic findings in the treatment group.

Misoprostol

Misoprostol, a prostaglandin E₁ analog, has been investigated as a preventive strategy against radiation proctitis. In a small prospective, randomized trial, Khan et al found that misoprostol rectal suppositories given prior to each radiotherapy session reduced acute and chronic proctitis symptoms.⁶² However, a subsequent and larger prospective randomized trial failed to show any significant differences in acute proctitis symptoms with misoprostol suppositories.⁶³ In addition, there was a higher incidence of rectal bleeding in the misoprostol group.

Endoscopic Thermal Therapy

Various endoscopic ablation therapies have been applied to the treatment of chronic proctitis-related bleeding due to local telangiectasias. The two most commonly utilized approaches are the Nd:YAG and argon lasers. Interestingly, there have been no prospective, randomized trials assessing either of these approaches. However,

several retrospective case series do exist. The largest series reporting on the use of the Nd:YAG laser found excellent response rates and a significant decrease in rectal bleeding.^{64,65} Rare complications included mucous discharge, ulcers, or stricture. Similarly, application of the argon laser has been reported in several series most commonly utilizing three treatment sessions. Again, all patients responded to some extent with all series noting a significant decrease in rectal bleeding and minimal complications.⁶⁶⁻⁶⁹ This also resulted in improved bowel function,⁶⁸ although more than 70% required maintenance treatment over the long term.⁶⁹

Formalin

Four percent formalin has been used for the treatment of bleeding related to chronic proctitis. Two approaches are commonly utilized: rectal formalin irrigation and topical application of formalin-soaked gauze. De Parades et al reported a prospective case series using the formalin gauze application and noted a beneficial result in 70%.⁷⁰ However, significant rates of stricturing and incontinence were reported. Numerous other retrospective series have reported good success with formalin. Among those using a gauze- or pledget-mediated application, at least a 75% success rate for cessation or improvement in bleeding was reported.⁷¹⁻⁷³ Many required multiple treatments, but complications were minimal. In those reporting use of formalin rectal irrigations, 50-mL aliquots were utilized up to a total volume of 400 to 500 mL. Again, a greater than 75% success rate was noted with this approach, with the most common reported complication being anal or pelvic pain, which occurred in 25% of those treated.^{74,75}

Hyperbaric Oxygen

There is low-level evidence supporting the use of hyperbaric oxygen treatments for chronic radiation proctitis. Treatment is usually undertaken at a pressure between 2 and 2.5 atmospheres and requires multiple treatments. Unfortunately, no prospective, randomized studies exist for this treatment approach, although there are numerous small retrospective case series. The largest and most recent report, involving 27 patients, found that two thirds had a partial or good response with respect to either bleeding, ulcer healing, or urgency.⁷⁶ However, none of the patients reported complete resolution with respect to pain. Other series have reported similar results with partial or complete response rates of 56% to 64% where most other methods of treatment had failed.^{77,78}

Antioxidant Vitamins

A single prospective series reported on the use of vitamins E and C for the treatment of chronic proctitis

after a minimum of 4 weeks of therapy.⁷⁹ The authors noted a significant improvement with respect to bleeding, diarrhea, and urgency, although subjects with rectal pain did not improve. Ten patients were followed up 1 year later and noted continued improvement in their symptoms.

Metronidazole

There is also a single prospective, randomized study evaluating the use of metronidazole along with anti-inflammatory agents (oral mesalazine and betamethasone enema) for chronic radiation proctitis.⁸⁰ After 4 weeks of treatment, the authors noted a significantly lower incidence of rectal bleeding and diarrhea in the metronidazole-treated group. This benefit persisted at 1 year after treatment.

Loperamide

The use of loperamide for the treatment of diarrhea related to chronic radiation enteritis was evaluated in a randomized, double-blind fashion.⁸¹ This medication was shown to decrease bowel frequency and improve bile acid absorption in this setting.

SURGICAL THERAPY

Despite the numerous medical approaches available for the treatment of radiation proctitis, surgical therapy remains another option for refractory cases. In addition, surgery may be required in the setting of obstruction, perforation, or fistula formation. Jao et al noted that 8.6% of patients with radiation proctitis required surgical intervention at a mean of 33 months after treatment.⁸² In a 30-year retrospective review, Pricolo and Shellito noted a general decrease in the number of surgical interventions performed over that time period.⁸³ The indications for surgery are most commonly rectum or rectosigmoid stenoses and rectovaginal fistulas, and the most common presenting symptoms are rectal bleeding, diarrhea, and tenesmus.^{82,84} The majority of these patients undergo diversionary procedures, with resection performed less commonly. Nonanastomosis resection procedures include proctectomy with colostomy, with or without a Hartmann rectal stump. When continuity is restored, a coloanal anastomosis utilizing a colonic J pouch with proximal covering stoma may be the procedure of choice in selected cases.⁸⁵ Successful outcomes with diversion alone are reported in the range of 72% to 73%.^{83,84} This approach is also useful in the setting of refractory rectal bleeding.⁸⁶ Although it has been suggested that the morbidity is less with simple diversion, which is thus safer than performing resection,^{82,84} Pricolo and Shellito found that this was not affected by the type of operation.⁸³ Overall, morbidity with surgical

intervention is extremely high, ranging from 30% to 65%.^{82,83} Mortality rates in the postoperative period are reported as 6.7% to 25%.⁸²⁻⁸⁴

CONCLUSION

Radiation injury to the lower GI tract is a common entity in the treatment of pelvic malignancy. Most commonly, injury is sustained to the rectum because of its fixed location. This toxicity is related to the total dose, frequency at which it is given, and the total volume of tissue irradiated. The effects can be acute (within 3 months), related to cell toxicity, or they can be chronic, occurring many years after completion of radiotherapy and related to a progressive vasculitis and ischemia. Symptoms are quite varied and include pain, cramping, bleeding, diarrhea, and tenesmus. Several scales are utilized to measure the toxic effects of radiotherapy. Although little is known about the specific incidence of radiation colitis, its prevention and management can be likened to those described for enteritis. Proctitis is far more common, and numerous preventive and treatment approaches have been utilized for medical management. These have been applied in both the acute and chronic settings, although few are universally successful. Surgery is reserved for refractory cases or for obstruction, perforation, or fistula. However, caution is required because of the morbidity and mortality of this approach. As radiotherapy continues to be an important component in the armamentarium against pelvic malignancy, future preventive medical strategies will be required to minimize this unfortunate toxicity.

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