The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Treatment of Chronic Radiation Proctitis

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The American Society of Colon and Rectal Surgeons (ASCRS) is dedicated to ensuring high-quality patient care by advancing the science, prevention, and management of disorders and diseases of the colon, rectum, and anus. The Clinical Practice Guidelines Committee is charged with leading international efforts in defining quality care for conditions related to the colon, rectum, and anus by developing clinical practice guidelines based on the best available evidence. These guidelines are inclusive, not prescriptive, and are intended for the use of all practitioners, healthcare workers, and patients who desire information about the management of the conditions addressed by the topics covered in these guidelines. Their purpose is to provide information on which decisions can be made rather than to dictate a specific form of treatment.

STATEMENT OF THE PROBLEM

Radiation therapy is frequently used in many types of cancer, including anal, cervical, prostate, and rectal. Although radiation has beneficial effects in treating tumors, collateral damage to the GI tract can occur, and although acute toxicity in the form of either proctitis or enteritis may occur, the more concerning symptom is the development of a chronic hemorrhagic radiation proctitis. Chronic hemorrhagic radiation proctitis is a syndrome marked by hematochezia, mucus discharge, tenesmus, and, often, fecal incontinence.[1] The incidence of this condition was previously reported to be as high as 30%[2]; however, with recent advances in radiation techniques, the delivery of a more targeted external beam radiation to tumors will hopefully minimize collateral toxicity. Current estimates are that ~1% to 5% of patients treated with radiation for pelvic malignancy will experience chronic radiation proctitis.[1] Because of the nature of the symptoms associated with this condition, colorectal surgeons are frequently called on for management and should be well versed in the various treatment options. This parameter will grade the evidence of the common interventions, which have been described for chronic hemorrhagic radiation proctitis.

METHODOLOGY

PubMed was used to search MEDLINE for all entries from January 1990 to October 26, 2017, with the results limited to human studies. Search terms included *radiation proctitis* (n = 757 titles), *radiation enteritis* (n = 492), *radiation proctitis* AND each of the following terms: *antibiotics* (n = 10), *argon beam* (n = 16), *aminosalicylate enema* (n = 5), *Carafate enema* (n = 16), *endoscopy* (n = 130), *formalin* (n = 90), *hyperbaric oxygen* (n = 56), *short chain fatty acid* (n = 15), and *steroid enema* (n = 13). The Cochrane Database of Systematic Reviews was searched with the term *radiation proctitis*. These searches yielded 1278 unique titles (PubMed = 1275, Cochrane = 3) that were screened, and 365 references were directly reviewed, ultimately yielding 56 references for inclusion. Prospective, randomized controlled trials and meta-analyses were given

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TABLE 1. The Grade of Recommendation, Assessment, Development, and Evaluation system: grading recommendations

	Description	*Benefit vs risk and burdens*	*Methodologic quality of supporting evidence*	*Implications*
1A	Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs without important limitations or overwhelming evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1B	Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens or vice versa	RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Strong recommendation, can apply to most patients in most circumstances without reservation
1C	Strong recommendation, low- or very low–quality evidence	Benefits clearly outweigh risk and burdens or vice versa	Observational studies or case series	Strong recommendation but may change when higher quality evidence becomes available
2A	Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient or societal values
2B	Weak recommendations, moderate-quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies	Weak recommendation, best action may differ depending on circumstances or patient or societal values
2C	Weak recommendation, low- or very low–quality evidence	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Observational studies or case series	Very weak recommendations, other alternatives may be equally reasonable

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RCT = randomized controlled trial.

preference in developing these guidelines. Directed searches of the embedded references from the primary articles were also performed in certain circumstances. The final source material used was evaluated for the methodologic quality, the evidence base was examined, and a treatment guideline was formulated by the subcommittee for this guideline. The final grade of recommendation was performed using the Grade of Recommendation, Assessment, Development, and Evaluation system[3] (Table 1). Members of the ASCRS Clinical Practice Guidelines Committee worked in joint production of these guidelines from inception to final publication. Recommendations formulated by the subcommittee were then reviewed by the entire Clinical Practice Guidelines Committee for edits and recommendations. Final recommendations were approved by the ASCRS Clinical Guidelines Committee and ASCRS Executive Committee. In general, each ASCRS Clinical Practice Guideline is updated every 3 to 5 years.

Evaluation of Chronic Radiation Proctitis

A disease-specific history and physical examination should be performed, emphasizing the degree and duration of bleeding. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.

The typical patient with chronic radiation proctitis (CRP) will present with hematochezia. Other common symptoms are fecal urgency, tenesmus, or drainage of mucus from the rectum.[1,2] It is important to review the history of the primary disease process and the radiation dose received. Because the most common indications for pelvic radiation therapy are malignancies (anal cancer, uterine cancer, cervical cancer, prostate cancer, and rectal cancer), it is important to assess the patient for recurrence of his or her primary cancer with physical examination or imaging where appropriate. At a minimum, a digital rectal examination should be performed to evaluate sphincter tone, as well as a proctoscopic examination to evaluate the quality of the mucosa, distribution of disease, and to rule out malignancy.[4] Colonoscopy is indicated if proctoscopy cannot delineate the full extent of disease, if it is impossible to rule out another form of colitis, or if the patient meets criteria for colonoscopy, as described by the US Multi-Society Task Force on Colorectal Cancers.[5]

Prophylactic measures, such as pedicled omental flap and tissue expander implant, have been described to decrease the incidence of radiation proctitis. These techniques are insufficiently evaluated and are not routinely recommended. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.

In the early 1990s, studies emerged describing methods to exclude the small bowel from the pelvis and to decrease the incidence of radiation enteritis. The first such study was a multicenter trial from Europe describing a mesh sling to exclude the small bowel from the pelvis before radiation.[6] There was no comparison group in this study, and the fear of complications from pelvic mesh has led to the abandonment of this approach. In the 1990s, pedicled omentoplasty was described.[7–9] Although this approach may reduce small-bowel enteritis, radiation proctitis was still seen in as many as 33% of patients.[8] Other strategies, such as tissue expander implant, have been described, but there is not sufficient evidence to support its use.[10] As radiation techniques have become more precise, it is thought that these adjuncts are not necessary to reduce complications.[11] Other adjuncts, such as oral glutamine during radiation, have been described. Although 1 study suggested decreased proctitis symptom severity in patients treated with glutamine,[12] another relatively recent randomized controlled trial suggested that the incidence of radiation proctitis in a modern series is low and that no benefit was derived from prophylactic glutamine administration.[13] Short chain fatty acid enemas given during radiation therapy were also studied in a randomized controlled trial and showed no benefit in preventing radiation proctitis.[14]

Medical Treatments

Formalin application is an effective treatment for bleeding in patients with CRP. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.

Formalin (ie, formaldehyde 4%–10%) has been used for >2 decades for the treatment of patients with CRP. The treatment can be rendered in the outpatient clinic setting with the patient awake or in a minor procedure room under intravenous sedation. Seow-Choen et al[15] reported their initial experience with 8 patients with hemorrhagic radiation proctitis. There were 7 women and 1 man, with a median age of 68 years. The median duration of symptoms before treatment was 8 months, with a median number of units of blood transfusion of 4 (range, 2 to 32). Bleeding resolved in 7 patients after 1 application, and 1 patient had an additional treatment at 2 weeks. No blood transfusion was required during a mean follow-up of 4 months.[15] Chautems et al[16] reported their experience with 13 patients who presented with hemorrhagic radiation-induced proctitis over a 10-year period. All of the patients were followed up to 1 year after treatment. In 8 patients, the bleeding resolved after the first application, and in 4 patients it required between 2 and 4 applications. One patient developed a mild asymptomatic rectal stricture.[16] Lee et al[17] reported their experience with a 4% formalin application. The mean duration of symptoms at presentation was 15.6 months. Improvement in symptoms and resolution of the bleeding were noted in the majority of patients after 1 treatment.[17] An additional study from Poland reported the outcome of 4% formalin application in 20 patients with radiation proctitis.[18] Most patients required an average of 2 treatments (range, 1–5). After the first application, 50% of the patients had complete resolution of the symptoms. In the remainder of patients, an additional formalin instillation, argon therapy, and/or 5-aminosalicylic acid suppositories were used to achieve remission.[18] The Cleveland Clinic Florida reported its experience with 4% formalin instillation for the treatment of radiation proctitis in 21 patients.[19] Bleeding stopped after the first treatment in 17 patients. The adverse effects noted were rectal pain in 4 patients, fecal incontinence in 2, and colitis in 1 patient.[19] Haas et al[20] reported their results with topical application of 10% buffered formalin. A total of 100 patients underwent the treatment. Cessation of bleeding was noted in 93% of the patients following a mean of 3.5 applications at 2- to 4-week intervals. Patients with severe proctitis and those on aspirin therapy required on average 1.5 additional treatments. Recurrent bleeding was noted in 8 patients, and all responded to additional formalin applications.[20] Luna-Pérez et al[21] reported their experience in 20 women with radiation proctitis refractory to topical steroids and/or mesalamine. A 4% formalin solution was used in 17 patients, and the bleeding resolved after the first application. Three patients needed repeat applications, with an overall success rate of 90% during a median follow-up of 20 months. Two patients developed rectovaginal fistula requiring colostomy with 1 subsequent abdominoperineal resection.[21]

Sucralfate retention enemas are a moderately effective treatment for rectal bleeding resulting from CRP. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.

In 1991, a prospective randomized, double-blind controlled trial of sucralfate enemas (2 g in 20 mL of water, twice daily) and oral sulfasalazine (1 g, 3 times daily) versus prednisolone enemas (20 mg in 20 mL of water, twice daily) and oral placebo, in 37 patients with symptomatic CRP, demonstrated clinical improvement in 94% and 53% of patients.[22] A subsequent study of 26 patients, all of whom were treated with a 10% sucralfate suspension in water administered twice daily, resulted in a significant decrease in rectal bleeding after 4 weeks of therapy, including negligible or complete cessation of bleeding in 23 patients (88%) after 16 weeks of therapy and no recurrent bleeding in 71% patients who were followed for a median of 45 months (range, 5–72 mo).[23] Two more recent studies, with 9 and 8 patients, who were treated with sucralfate enema (2 g in 20–50 mL of water or saline), demonstrated rectal ulcer with healing or alleviation of bleeding in 89% and 100% of patients.[24,25] In a recent study of 23 patients, a 6-week course of sucralfate paste enemas (2 g of sucralfate mixed with 4.5 mL of water, twice daily) resulted in

a partial improvement in a composite score of radiation proctitis symptoms (ie, bleeding, urgency, frequency, and cramping) in 41% and complete resolution of all symptoms in 32%.[26]

Short chain fatty acid enemas are not effective in preventing or treating chronic hemorrhagic radiation proctitis and are not recommended. Grade of Recommendation: Weak recommendation based on moderate-quality evidence, 1B.

There has been some interest in short chain fatty acids such as butyrate to treat radiation proctitis. The limited studies in treating chronic hemorrhagic proctitis have not been conclusive. Although some studies have demonstrated no clear benefit,[27,28] 1 randomized controlled trial showed superior symptom relief and mucosal healing compared with placebo.[29] However, the enema treatments needed to be given for 5 weeks to achieve this result, and the beneficial effects dissipated once the treatment was ceased.[29] Short chain fatty acids have been studied with reasonable clinical improvements in acute radiation proctitis, but have not been shown to decrease the incidence of chronic hemorrhagic radiation proctitis.[14,30,31]

Alternative treatments such as mesalamine, ozone therapy, and metronidazole have not been adequately evaluated in treating radiation proctitis and are not recommended. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.

Many alternative treatments, such as mesalamine,[32,33]ozone therapy,[34] and metronidazole,[35] have been described in the treatment of radiation proctitis. These treatments have not been thoroughly evaluated and are not recommended in the treatment of CRP.

Interventional Treatments

Endoscopic argon beam plasma coagulation is a safe and effective treatment for rectal bleeding induced by CRP. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.

In patients with rectal bleeding from CRP, endoscopic argon beam plasma coagulation (APC) therapy results in cessation or a meaningful decrease in bleeding in 79% to 100% of patients.[36–43] A median of 2 APC sessions (range, 1–5) is typically required to control rectal hemorrhage. A randomized trial of APC versus topical formalin application conducted in 30 patients with bleeding CRP demonstrated control of bleeding in 94% and 100% (p value not significant) and no difference in relief of other CRP symptoms.[40] Rectal pain, mucus discharge, and rectal ulcerations commonly occur after APC but infrequently require intervention and are most often self-limited. Severe complications, including rectovaginal fistula and rectal stricture, occur infrequently, with ≈3% of patients affected.[39,41–43] The effectiveness of APC for the relief of fecal urgency and frequency in patients with CRP is limited, but 2 prospective studies have demonstrated improvement of these symptoms,[36,44] and another showed no benefit or harm.[40] Despite rare reports of colonic explosion with perforation during APC after retrograde enema preparation of the rectum,[37] the use of retrograde enema, complete antegrade bowel preparation, or no bowel preparation, all appear to be safe for rectal APC procedures.[38,40,43] In most studies, argon flow of 1 to 2 L per minute, at a power of 40 to 60 watts, and application to the rectal mucosa in pulses of 1 to 2 seconds have been described.

Hyperbaric oxygen therapy is an effective treatment modality to reduce bleeding in patients with CRP. Grade of Recommendation: Strong recommendation based on moderate-quality evidence, 1B.

Hyperbaric oxygen therapy (HBOT) has emerged as an effective treatment for nonhealing wounds from various etiologies including traumatic, postoperative, diabetic related, or radiation induced.[45] The impact of HBOT on tissue healing is postulated through improving tissue oxygenation and possible angiogenic and antibacterial effects. Woo et al[46] evaluated 18 patients with CRP. Of 13 patients with rectal bleeding, 4 patients had complete resolution and 3 had some improvement.[46] Kitta et al[47] from Japan reported the outcome of 4 patients with radiation proctitis after treatment of prostate cancer. Although patients had a significant reduction in degree of bleeding, 1 patient relapsed 3 months after completion of therapy, 1 continued to have minor rectal bleeding, and 1 continued to have persistent proctalgia with no rectal bleeding.[47] Another study examined the outcome of 10 patients, including 3 men and 7 women, with CRP treated by HBOT.[48] HBOT was well tolerated, and 9 of the 10 patients completed the full course of 40 treatments. During a median follow-up period of 25 months, rectal bleeding stopped in 4 patients and improved in 3 others. There was symptomatic improvement in bleeding, diarrhea, and rectal pain in the majority of patients. Only 2 of the 10 patients had no response.[48] Similarly, Oscarsson et al[49] conducted a prospective cohort study to assess the effectiveness of HBOT in patients with CRP. Thirty-nine patients (35 men and 4 women, mean age of 71 y) were evaluated. The mean number of treatment was 36 sessions. The symptoms of CRP were alleviated in 89% of the patients.[49] A randomized, controlled, double-blind crossover trial was conducted by Clarke et al[50] to assess the long-term effectiveness of HBOT in patients with refractory radiation proctitis. The patients were randomly assigned to HBOT (100% oxygen at 2.0 atmospheres, group 1) versus air (21% oxygen at 1.1 atmospheres, group 2). Patients in group 2 were subsequently crossed to group 1. Symptoms were assessed at

3 and 6 months and then at year 1 to 5. Of 150 patients enrolled in the study, 120 patients were evaluable. The amount of improvement was nearly twice as great in group 1, which had a greater portion of responders (88.9% vs 62.5%; $p = 0.009$). In group 2, the differences were abolished after crossover.[50] Virginia Mason Medical Center reported its experience with HBOT for patients treated for prostate cancer with radiotherapy. Over a 5-year period, 27 patients received HBOT (average of 36 sessions; range, 29 to 60 sessions). Complete resolution of bleeding was noted in 48% of patients, and 28% reported fever bleeding episodes. Fecal urgency resolved in 50% of the patients. Of patients with rectal ulcers on endoscopy, complete resolution was noted in 21%, and 29% had some improvement. In this study, only 33% of the patients had no response.[51] Although there is a clear benefit to HBOT in patients with CRP, it is an expensive therapy that requires specialized equipment and several weeks of treatment sessions; thus, it is not widely available.

Endoscopic bipolar electrocoagulation, radiofrequency ablation, Nd-YAG laser, and cryotherapy are alternative treatments of rectal bleeding from CRP that have been insufficiently evaluated and are thus not recommended. Grade of Recommendation: Strong recommendation based on low-quality evidence, 1C.

A recent randomized prospective trial of bipolar electrocoagulation or APC for the treatment of rectal bleeding attributed to CRP demonstrated equal efficacy in bleeding control (92% vs 93%) but significantly more complications in the bipolar electrocoagulation group (87% vs 33%).[52] Endoscopic radiofrequency ablation is an emerging technology that, in 2 retrospective studies, resulted in control of CRP rectal bleeding in 94% and 100% of patients.[53,54] Despite limited evidence in support of the use of endoscopic Nd-YAG laser[55] or cryotherapy,[56] uncertainty of the efficacy and safety of these techniques should preclude their routine use in patients with bleeding CRP.

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