Communication from the ASGE Standards of Practice Committee

GUIDELINE

ASGE guideline on the role of endoscopy for bleeding from chronic radiation proctopathy

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This document was reviewed and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy (ASGE)

Chronic radiation proctopathy is a common sequela of radiation therapy for malignancies in the pelvic region. A variety of medical and endoscopic therapies have been used for the management of bleeding from chronic radiation proctopathy. In this guideline, we reviewed the results of a systematic search of the literature from 1946 to 2017 to formulate clinical questions and recommendations on the role of endoscopy for bleeding from chronic radiation proctopathy. The following endoscopic modalities are discussed in our document: argon plasma coagulation, bipolar electrocoagulation, heater probe, radiofrequency ablation, and cryoablation. Most studies were small observational studies, and the evidence for effectiveness of endoscopic therapy for chronic radiation proctopathy was limited because of a lack of controlled trials and comparative studies. Despite this limitation, our systematic review found that argon plasma coagulation, bipolar electrocoagulation, heater probe, and radiofrequency ablation were effective in the treatment of rectal bleeding from chronic radiation proctopathy. (Gastrointest Endosc 2019;90:171-82.)

(footnotes appear on last page of article)

INTRODUCTION

Bladder, cervical, prostate, and rectal cancers are among the most commonly diagnosed cancers in the United States, with an estimated 300,000 new cases in 2019.[1] Radiation therapy is an essential component of adjuvant, neoadjuvant, curative, or palliative therapy for cancers in these sites. Despite advances in radiation science, up to 30% of patients who undergo radiation therapy for pelvic malignancies will develop and suffer from radiation proctopathy.[2-5]

Radiation proctopathy is broadly defined as epithelial damage to the rectum from radiation therapy and can be categorized as acute or chronic, based on the timing of symptom development. *Acute radiation proctopathy* develops during or within 3 months of radiation therapy and is characterized by superficial epithelial cell depletion with acute inflammatory infiltrate in the lamina propria.[6,7] In contrast, *chronic radiation proctopathy* develops at least 3 months after radiation therapy, with a median time between 8 and 12 months, and is characterized by obliterative or ischemic endarteritis of the submucosal arterioles, submucosal fibrosis, and neovascularization.[8,9] A key distinction between acute and chronic radiation proctopathy is the relative lack of inflammatory infiltrate in the latter.

Acute radiation proctopathy often presents with abdominal or pelvic pain, tenesmus, diarrhea, or urgency and is usually self-limiting. Rectal bleeding and fecal incontinence occur less commonly. *Chronic radiation proctopathy* can manifest with any of the acute symptoms that persist past 3 months or with rectal bleeding, fecal incontinence, or symptoms from stricture or fistula development. Endoscopy is the main tool to establish a diagnosis and helps determine the extent and severity of disease. Endoscopic findings include pallor, edema, and friability of the mucosa, along with spontaneous bleeding and telangiectasias. Although biopsy specimens can be taken to rule out other causes of proctitis (eg, infection, inflammatory bowel disease), they are discouraged because of the possibility of the biopsy sampling creating nonhealing ulcers or fistulas.[10-12]

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A variety of treatments have been described for the management of acute and chronic radiation proctopathy over the past few decades, including medical, endoscopic, and surgical approaches. Most cases of acute radiation proctopathy respond to hydration, antidiarrheal medications, and discontinuation of radiation therapy. In contrast, medical or supportive therapy may not be effective or sufficient in reducing symptoms from chronic radiation proctopathy, particularly rectal bleeding. Therefore, endoscopic therapy has become a widely used treatment method for the management of chronic radiation proctopathy.

AIM AND SCOPE

The aim of this document is to provide evidence-based recommendations on endoscopic therapy in the management of bleeding from chronic radiation proctopathy. The following endoscopic modalities are discussed: argon plasma coagulation (APC), bipolar electrocoagulation, heater probe, radiofrequency ablation (RFA), and cryoablation. This document is a revision of a previous American Society for Gastrointestinal Endoscopy (ASGE) guideline.[13]

METHODS

Overview

This document was prepared by a working group of the Standards of Practice Committee of the ASGE. It includes a systematic review of available literature and published guidelines for the role of endoscopy in the management of chronic radiation proctopathy using criteria highlighted in Table 1.[14] After evidence synthesis, recommendations were drafted by the full panel during a face-to-face meeting on March 16, 2018 and subsequently approved by the Standards of Practice committee members and the ASGE Governing Board.

Panel composition and conflict of interest management

The panel consisted of 2 content experts (J.K.L., D.A.), a committee member with expertise in systematic reviews and meta-analysis (N.C.T.), the committee chair (S.B.W.), and other committee members. All panel members were required to disclose potential financial and intellectual conflict of interest, which were addressed according to ASGE policies set forth in the ASGE Conflict of Interest and Resolution Policy (at https://www.asge.org/docs/default-source/about-asge/mission-and-governance/asge-conflict-of-interest-and-disclosure-policy.pdf?sfvrsn=2) and the publication-specific policy and form included in Conflict of Interest Principles for ASGE Publications and Educational Product Development excluding Gastrointestinal Endoscopy and CME activity (at https://www.asge.org/docs/default-source/about-asge/mission-and-governance/doc-asge-publications-coipolicy_2009.pdf?sfvrsn=6).

Formulation of clinical questions

For all clinical questions, potentially relevant patient-important outcomes were identified a priori and rated from "not important" to "critical" through a consensus process. Our main clinical question was the effectiveness of each endoscopic therapy compared with other interventions for the treatment of bleeding from chronic radiation proctopathy. Clinical success was defined as bleeding cessation, improvement in hemoglobin by 10% or normalization, bleeding score improvement, or eradication of telangiectasias. Other clinical outcomes of interest were rates of overall and severe adverse events. We defined severe adverse events a priori as colonic fistula, perforation, explosion, or stricture.

Literature search and study selection criteria

To inform this guideline, a comprehensive literature search was performed by a medical librarian using Ovid Medline entries from 1946 to January 2017 and Embase entries from 1988 to January 2017. The searches were limited to English language articles with animal studies excluded. Because of the large number of case reports, we restricted our eligibility criteria to only include case series with more than 5 patients. The full literature search strategy is demonstrated in Appendix 1 (available online at www.giejournal.org).

For each treatment modality a literature search for existing systematic reviews and meta-analyses was also performed. If none was identified, a full systematic review and meta-analysis (when possible) was conducted using the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria.[15] Details of the search strategy are reported in Appendix 1. Citations were imported into EndNote (Thompson Reuters, Philadelphia, Pa), and duplicates were removed. The EndNote library was then uploaded into Covidence (www.covidence.org). Two authors (J.K.L., D.A.) first screened the studies by title and abstract and then by full text, and all conflicts were resolved by consensus. If existing systematic reviews and meta-analyses were available, inclusion and exclusion criteria were reviewed, and methodologic quality of the study was assessed using the measurement tool to assess systematic reviews (Assessing the Methodological Quality of Systematic Reviews 2; available at https://amstar.ca/Amstar_Checklist.php). Only systematic reviews and meta-analyses meeting the quality thresholds were used for our data synthesis. When applicable, available systematic reviews and meta-analyses were updated based on literature review as described above.

Data extraction and statistical analysis

If data extraction was needed for a meta-analysis, data were extracted by 2 independent reviewers using Microsoft Excel (Microsoft Corporation, Redmond, Wash). The primary estimate of effect was based on a priori identified outcomes of interest. For outcomes with limited or no

TABLE 1. System for rating the quality of evidence for guidelines

Categories	Meaning	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of effect.	Future research is very unlikely to change our confidence in the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.	Further research is likely to have an impact on our confidence in the estimate of the effect and may change the estimate.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect.	Further research is very likely to have an impact on our confidence in the estimate of the effect and is likely to change the estimate.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.	Any estimate of the effect is very uncertain.

Adapted from Guyatt et al.[14]

available direct comparisons, indirect comparisons were used to estimate the magnitude and direction of effect. Heterogeneity was assessed using the I^2 and Q statistic. Significant heterogeneity was defined at $I^2 > 50\%$ and significant P value (<.05) on the Q statistic. Random-effects models were used if significant heterogeneity was detected. Otherwise, fixed-effects models were used. Studies were weighted based on their size. Statistical analyses were performed using Comprehensive Meta Analysis V3 (Biostat Inc, Englewood, NJ).

Certainty in evidence (quality of evidence)

The certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest on the following domains: risk of bias, precision, consistency and magnitude of the estimates of effects, directness of the evidence, risk of publication bias, presence of dose–effect relationship, and an assessment of the effect of residual, opposing confounding.

Considerations in the development of recommendations

During an in-person meeting, the panel developed recommendations based on the following criteria, if available: the certainty in the evidence, the balance of benefits and harms of the compared management options, values and preferences of the patients, resource utilization, and cost-effectiveness. The final wording of the recommendations (including direction and strength), remarks, and qualifications were decided by consensus using criteria highlighted in Table 1,[14] and were approved by all members of the panel. The strength of individual recommendations is based on the aggregate evidence quality and an assessment of the anticipated benefits and harms. Stronger recommendations are typically stated as "we recommend…," whereas weaker recommendations are indicated by phrases such as "we suggest…." Table 2 provides the suggested interpretation of strong and conditional recommendations by patients, clinicians, and healthcare policymakers.

Patient values and preferences and cost-effectiveness

Currently, there are no data regarding patient preferences with regard to medical or endoscopic strategies for the management of chronic radiation proctopathy. In addition, there are no resource utilization or cost-effectiveness studies evaluating medical versus endoscopic therapy or different endoscopic modalities for the management of chronic radiation proctopathy.

RESULTS

Endoscopic therapies for bleeding from chronic radiation proctopathy

This document focuses on currently available endoscopic therapies for managing patients with chronic radiation proctopathy, which include APC, bipolar electrocoagulation, heater probe, RFA, and cryoablation. Highly variable definitions for clinical success were described in the literature describing the effectiveness of endoscopic therapies for chronic radiation proctopathy. In addition, not all studies used a standardized grading or scoring system to determine therapeutic success. Therefore, as stated in Methods, we broadly defined clinical success as bleeding cessation, improvement in hemoglobin by 10% or normalization, bleeding score improvement, or eradication of telangiectasias. Despite our broad and comprehensive search, limited high-quality randomized trials or comparative effectiveness studies were available to inform our guideline document.

The recommendations, quality of evidence, and strength of recommendations are summarized in Table 3. The panel members recommend that before embarking on endoscopic therapy for radiation proctopathy, patients should have a clear understanding of the risks, benefits, and alternatives to endoscopic therapy. The panel members agreed that before using endoscopic therapy for radiation proctopathy, the endoscopist should obtain informed consent that includes a discussion on the natural

TABLE 2. Interpretation of definitions of strength of recommendation using Grading of Recommendations Assessment, Development and Evaluation framework

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policymakers	The recommendation can be adopted as policy in most situations. Compliance with this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders.

Adapted from Andrews et al.[70]

TABLE 3. Recommendations

Statement	Strength of recommendation	Quality of evidence
1. In patients with chronic radiation proctopathy, we suggest argon plasma coagulation, bipolar electrocoagulation, heater probe, and radiofrequency ablation for treatment of bleeding from chronic radiation proctopathy. There is insufficient evidence to recommend a specific endoscopic modality over another for treatment of bleeding from chronic proctopathy.	Conditional	Low
2. In patients with chronic radiation proctopathy, we suggest against the use of 4% formalin compared with argon plasma coagulation because of higher adverse event rates compared with argon plasma coagulation for treatment of bleeding from chronic radiation proctopathy.	Conditional	Low
3. In patients with chronic radiation proctopathy, there is insufficient evidence for or against the use of the newer-generation cryoablation system for treatment of bleeding from chronic radiation proctopathy.		

history of chronic radiation proctopathy, treatment options, risks and benefits of each approach, the frequency of endoscopic therapy sessions, and duration of follow-up. There is no mandate for treating "cosmetic" rectal bleeding (ie, minor rectal bleeding without anemia) given the lack of studies to date to support endoscopic management for this indication. Patient preferences, comorbidities, life expectancy, and locally available endoscopic therapies should be considered in the management algorithm of these patients.

Argon plasma coagulation

APC is a widely used endoscopic therapy for chronic radiation proctopathy because of its availability in most endoscopy units, portability, and the ability to apply noncontact thermal therapy in tangential locations. APC therapy for chronic radiation proctopathy is delivered using the tip of the APC probe passed through the endoscope with short noncontact application periods of 1 to 2 seconds to the target tissue (Appendix 1). Care should be taken to target treatment on individual vessels and avoid "painting" with APC, which can lead to large confluent ulcers.

In our systematic review we found 33 studies that reported the efficacy of APC for rectal bleeding on a total of 957 patients with chronic radiation proctopathy (Table 4).[16-48] Among the 33 studies, 3 compared APC with other endoscopic modalities or medical therapy.[16,29,46] Specifically, 2 studies compared APC with 4% topical formalin[16,46] and 1 study assessed APC versus bipolar electrocoagulation.[29] A pooled analysis of all 33 studies found an overall clinical success rate of 87% (95% confidence interval, 85%-90%) with an $I^2 = 32$ (Fig. 1), indicating low heterogeneity among the studies. The mean or median number of treatment sessions for APC to achieve bleeding control ranged from 1 to 3.7. The time interval between treatment sessions ranged from 2 to 8 weeks; most studies reported a 3- to 4-week interval to allow enough time for the injured mucosa to heal. APC settings from our review reported a power ranging from 25 to 80 W (median, 50 W) and an argon flow rate of .6 to 2.5 L/min (median, 1.5 L/min). When stratified by differences in APC flow rate settings, treatment success rates were fairly similar at 87% and 86% using a flow rate of $\leq$1 L/min and >1 L/min, respectively. However, most studies in this systematic review used the first-generation APC machine (ICC/APC 300 system; Erbe Elektromedizin, Tuebingen, Germany), which may not be available in most endoscopy units.[16,18,19,21,24-26,28,29,32,33,37,39,40,44,46,48] Only 3 studies used the second-generation APC machine (VIO APC/APC 2; Erbe Elektromedizin).[17,31,46]

Comparative studies. APC appears to be more or at least equally effective to 4% formalin for the management of bleeding from chronic radiation proctopathy. In a study

by Yeoh et al,[46] 30 patients with intractable rectal bleeding (defined as 1 episode per week or more or requiring blood transfusions or both despite medical therapy) from chronic radiation proctopathy were randomized to either APC or 4% topical formalin. Bleeding cessation was seen in 94% of patients treated with APC (median treatment sessions, 2) versus 100% of patients treated with topical formalin (median treatment sessions, 2). There were no significant differences in efficacy and durability of bleeding cessation between the 2 groups. Both treatments were well tolerated without any adverse events. APC was also compared with topical 4% formalin in a cohort study of 25 patients with rectal bleeding from chronic radiation proctopathy.[16] Clinical success was defined as improvement of hemoglobin by 10% or normalization of hemoglobin levels. Eleven of 14 patients (79%) had clinical success from APC compared with 3 of 11 patients (27%) treated with formalin ($P = .017$). The mean number of treatment sessions was similar with both APC and 4% formalin (1.7 sessions vs 1.8 sessions, respectively). However, the APC group had fewer adverse events (ie, nausea, vomiting, rectal pain, and fever) compared with the formalin group (36% vs 82%, $P = .001$).

APC appears to be equally effective as bipolar electrocoagulation for the management of rectal bleeding in chronic radiation proctopathy. In a randomized study of 30 patients with recurrent rectal bleeding from chronic radiation proctopathy, there were no significant differences in clinical success (defined as eradication of all telangiectasias) with APC compared with bipolar electrocoagulation (93% vs 80%, $P = .6$) or mean number of sessions needed for eradication (3.7 vs 2.9, $P = .3$) in the intention-to-treat analysis.[29] However, there was a higher, although not statistically significant, rate of bleeding during treatment from ulcers with bipolar electrocoagulation compared with APC (33.3% vs 6.7%, $P = .17$). During a mean follow-up of 12.5 months (range, 3-30), there was no difference in relapse rate of rectal bleeding between the 2 groups (8% vs 14%, $P = 1.0$).

Adverse events. The reported rate of adverse events with APC is variable,[16-48] likely because of the lack of standard APC settings, variation in the criteria for defining adverse events, and variable follow-up periods. After determining an a priori definition for serious adverse events (ie, colonic fistula, perforation, explosion, or stricture), we found the pooled serious adverse event rate to be 4% (95% confidence interval, 3%-6%) with an $I^2 = 0$, indicating low heterogeneity between studies. The most common APC-related adverse event was abdominal, rectal, or anal pain, which could be related to ulcerations caused by the treatment itself or excessive bowel distention from the quick instillation of argon gas. Therefore, the insufflated argon gas should be removed periodically to help alleviate the pain from bowel distension and potentially mitigate the risk of postprocedural discomfort. Colonic explosions have also been reported in 2 poorly prepped patients who only received an enema preparation before APC therapy.[19,28] Therefore, adequate bowel preparation is needed before initiating APC therapy.

Bipolar electrocoagulation

Bipolar electrocoagulation is a contact treatment method for chronic radiation proctopathy. In our systematic review, we found 4 studies that reported the efficacy of bipolar electrocoagulation for rectal bleeding on a total of 96 patients with chronic radiation proctopathy (Table 5).[29,49-51] Only 2 studies compared bipolar electrocoagulation with other endoscopic modalities or medical therapy; 1 compared bipolar electrocoagulation with APC[29] and another study assessed bipolar electrocoagulation versus heater probe.[49] A pooled analysis of all 4 studies[29,49-51] from our systematic review found an overall clinical success rate of 88% (95% confidence interval, 68%-96%) with an $I^2 = 54$ (Fig. 2), indicating moderate heterogeneity between studies. The mean or median number of treatment sessions for bipolar electrocoagulation ranged from 2.9 to 4 to achieve bleeding control. The time interval between treatment sessions ranged from 4 to 6 weeks.

Comparative studies. Bipolar electrocoagulation appears to be as equally effective as a heater probe for the management of rectal bleeding in patients with chronic radiation proctopathy. In a randomized trial involving 21 patients with recurrent hematochezia and anemia because of chronic radiation proctopathy, Jensen et al[50] showed that bipolar electrocoagulation and heater probe had similar clinical success rates for bleeding control (75% vs 67%) after 12 months of follow-up. No major adverse events were reported in the trial at the end of follow-up. Bipolar electrocoagulation also appears to be as equally effective as APC for the management of rectal bleeding in chronic radiation proctopathy (described in Argon Plasma Coagulation, above).[29]

Adverse events. Data on serious adverse event rates with bipolar electrocoagulation are limited. Lenz et al[29] reported that 5 of 15 patients (33%) who underwent bipolar electrocoagulation had worsening rectal bleeding either during or after the procedure. In addition, 4 of 15 patients (27%) developed rectal stenosis, only 1 of whom had symptoms. In the study of Jensen et al,[50] none of the 12 patients developed any serious adverse events with bipolar electrocoagulation after 12 months of follow-up. There have been no reports of perforation or fistula formation after bipolar electrocoagulation for chronic radiation proctopathy.

Heater probe

Heater probe is a contact treatment method for chronic radiation proctopathy. Unlike bipolar electrocoagulation, heater probe mucosal injury is based on direct heat application rather than electrical current. In our systematic review, we found 2 studies on the efficacy of heater probe for chronic radiation proctopathy (Table 5).[50,52] In a case series of 8 patients with rectal bleeding, all patients had

TABLE 4. Summary of studies using argon plasma coagulation for chronic radiation proctopathy

First author, year	Type of study	No. of patients	Gender (M/F)	Age (y)	Flow rate (L/min)	Power setting (W)	No. of treatment sessions
Alfadhli, 2008[16]	Case series	14	11/3	74.7 (mean)	1.2-2.0	45-50	1.78 (mean)
Al Gizaway, 2012[17]	Case series	17	NR	55 (median)	.8-1.0	40-50	NR
Alvaro-Villegas, 2011[18]	Case series	14	NR	59.3 (mean)	1.6	60	3 (mean)
Ben-Soussan, 2004[19]	Case series	27	19/8	73.1 (mean)	.8-1.0	40-50	2.7 (mean)
Canard, 2003[20]	Case series	30	23/7	70.7 (mean)	.8-2.0	30-80	2.3 (mean)
Chrusciewska-Kiliszek, 2013[21]	Randomized trial	122	59/63	65.5 (mean)	1.0-2.0	25-40	2.3 (mean)
Cunha, 2016[22]	Cohort study	43	NR	NR	1.2	40	2.63 median
Dees, 2006[23]	Case series	50	46/4	73.6 (mean)	2	50	3 (median)
De la Serna Higuera, 2004[24]	Case series	10	3/7	67.5 (mean)	1.5-2.0	60	1.7 (mean)
Fantin, 1999[25]	Case series	7	6/1	76.3 (mean)	3	60	2.4 (mean)
Hortelano, 2014[26]	Case series	30	30	70 (median)	1.8	50	3 (median)
Kaassis, 2000[27]	Case series	16	NR	73.5 (mean)	.6	40	3.7 (mean)
Karamanolis, 2009[28]	Case series	56	NR	68.4 (mean)	2	40	2 (mean)
Lenz, 2011[29]	Randomized trial	15	8/7	70.4 (mean)	1	40	3.7 (mean)
López-Arce, 2010[30]	Case series	19	10/9	64 (median)	1.0-1.5	40-50	2.0 (median)
Onoyama, 2011[31]	Case series	24	24	74.8 (mean)	1	30-40	NR
Rolachon, 2000[32]	Case series	12	NR	70.3 (mean)	1	50	2.8 (mean)
Rotondano, 2003[33]	Case series	24	5/19	69.2 (mean)	.8-1.2	40	2.5 (median)
Sait Dag, 2013[34]	Case series	21	7/14	61.8 (mean)	1.2-2.0	40-60	3 (mean)
Sebastian, 2004[35]	Case series	25	24/1	69 (mean)	1.5	25-50	1 (median)
Silva, 1999[39]	Case series	28	4/24	65 (mean)	1.5	50	2.9 (median)
Siow, 2017[37]	Case series	91	85/6	58.2 (mean)	1.5-2.0	50	1.9 (mean)
Swan, 2010[38]	Case series	50	45/5	72.1 (mean)	1.4-2.0	50	1.4 (mean)
Taïeb, 2001[39]	Case series	11	10/1	73 (mean)	.8-2.0	50	3.2 (mean)
Tam, 2000[40]	Case series	15	14/1	NR	2	60	2 (median)
Tjandra, 2001[41]	Case series	12	10/2	71.3 (mean)	1.5	40	1.8 (mean)
Tomasello, 2012[42]	Case series	16	NR	NR	NR	NR	NR
Venkatesh, 2002[43]	Case series	40	NR	NR	1.0-1.5	40-60	1.4 (mean)
Villavicencio, 2002[44]	Case series	21	15/6	72.6 (median)	1.2-2.0	45-50	1.7 (mean)
Weiner, 2017[45]	Case series	35	NR	NR	NR	NR	2 (median)
Yeoh, 2013[46]	Randomized trial	17	17 M	73 (mean)	2	60-80	2 (median)
Zan, 2011[47]	Case series	31	NR	NR	NR	NR	2.4 (mean)
Zinicola, 2003[48]	Case series	14	10/4	68 (mean)	2	65	1.5 (mean)

NR, Not reported; *Hgb*, hemoglobin.

clinical success (defined as complete bleeding cessation or diminished bleeding) and improvement of blood counts after heater probe therapy.[52] The number of treatment sessions ranged from 1 to 4 with an intensity of 200 to 400 joules per session. The time interval between treatment sessions ranged from 4 to 6 weeks.

TABLE 4. Continued

Time interval between treatment sessions	Follow-up time (mo)	Endpoint	Efficacy	Change in Hgb	Score	Serious adverse events
NR	NR	Clinical response (10% increase in Hgb or normalization of Hgb)	11/14 (78.6%)	10.6 → 12.6	NR	0/14
2 wk	37 (median)	Bleeding cessation	14/17 (82.4%)	NR	NR	NR
NR	3 (mean)	Improvement in Hgb levels	12/14 (85.7%)	9.9 →11.2	NR	0/14
5 wk	13.6 (mean)	Bleeding cessation	25/27 (92%)	NR	NR	3/27
NR	20 (mean)	Bleeding score improvement	26/30 (87%)	NR	2.67 → .77	1/30
8 wk	11	Change in disease severity score	122/122 (100%)	NR	NR	2/122
30 days	11.4 (mean)	Bleeding cessation	43/43 (100%)	NR	NR	0/41
3 wk	NR	Insignificant or absent blood loss AND no recurrence of anemia	47/48 (98%)	NR	NR	0/50
3-4 wk	31.1 (mean)	Bleeding cessation	10/10 (100%)	NR	NR	0/10
3 wk	25.7 (mean)	Bleeding cessation	7/7 (100%)	NR	NR	0/7
3-4 wk	14.5 (median)	Bleeding cessation	23/30 (77%)	NR	NR	0/30
4 wk	10.7 (mean)	Bleeding cessation	16/16 (100%)	NR	2.4 → 0.6	0/16
3-4 wk	17.9 (mean)	Bleeding cessation	50/56 (89%)	NR	NR	1/56
30 days	12.5 (mean)	Eradication of telangiectasia	12/15 (80%)	NR	NR	0/15
3 wk	29 (median)	Bleeding cessation	19/19	11.8 → 12.9	2.2 → 0	0/19
NR	NR	Bleeding cessation	24/24 (100%)	10.0 → 12.3	NR	NR
NR	6	Bleeding cessation	10/12 (83%)	NR	NR	1/12
4 wk	41 (median)	Bleeding cessation	24/24 (100%)	9.2 → 12.8	2.9 → .8	2/24
2 wk	NR	Therapeutic response (decrease in frequency and severity of rectal bleeding)	18/21 (86%)	NR	NR	0/21
NR	14 (median)	Bleeding cessation	25/25 (100%)	10.05 → 12.44	3.0 → .0	0/25
4 wk	10 (mean)	Bleeding cessation	28/28	Mean Hgb increased by 1.2 g/dL	3.0 → .78	0/28
NR	13.1 (mean)	Bleeding cessation	72/91 (79.1%)	NR	NR	3/91
NR	20.6 (mean)	Bleeding reduction by symptom score	49/50 (98%)	NR	NR	1/50
1 mo	19 (mean)	Bleeding cessation	9/11 (82%)	7.7 →11.5	NR	2/11
NR	24 (median)	Improvement in rectal bleeding score	15/15 (100%)	10.8 → 13.3	3.0 → 1.0	2/15
NR	10.7 (mean)	Bleeding cessation	10/12 (83%)	11.2 → 12.3	NR	0/12
NR	NR	Bleeding cessation	16/16 (100%)	NR	NR	0/16
3 wk	NR	Bleeding cessation	39/40 (98%)	NR	NR	0/40
NR	10.5 (median)	Bleeding cessation	20/21 (95%)	NR	NR	0/21
NR	56 (median)	Bleeding cessation	30/35 (86%)	NR	NR	2/35
NR	110 (median)	Bleeding cessation	16/17 (94%)	NR	3.0 → 1.0	0/17
NR	NR	Hemorrhage intensity by means of evaluation score, Hgb level	NR	11.8 → 13.4	3.3 → .1	0/31
NR	13 (mean)	Bleeding cessation	12/14 (86%)	NR	2.6 → .9	1/14

Comparative studies. Only 1 randomized trial has compared heater probe with bipolar electrocoagulation for chronic radiation proctopathy, which we have described in detail above (see Bipolar Electrocoagulation).[50]

Adverse events. Based on our systematic review, no serious adverse events have been reported with use of heater probe therapy for rectal bleeding in patients with chronic radiation proctopathy.

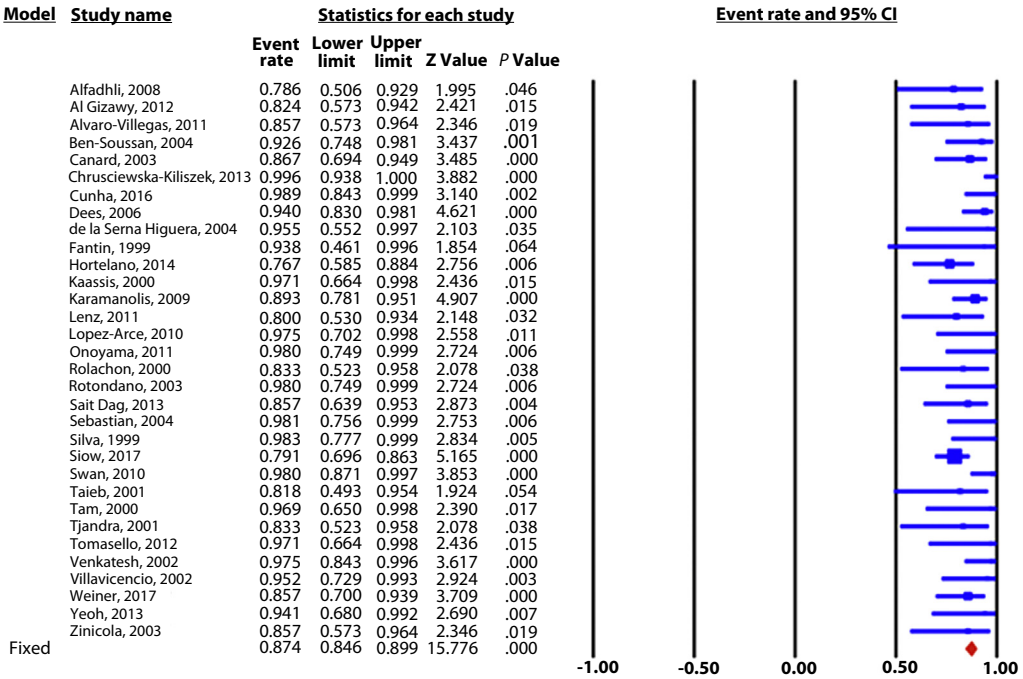

Figure 1. Forest plot of studies assessing clinical success of argon plasma coagulation for bleeding from chronic radiation proctopathy. *CI*, Confidence interval.

Radiofrequency ablation

RFA is a contact treatment method for chronic radiation proctopathy that has been well described for the treatment of Barrett's esophagus.[53-55] RFA allows the depth of penetration to ablate the epithelium and muscularis mucosa without injuring the submucosa. RFA for chronic radiation proctopathy is performed using a single-use focal ablation electrode catheter (HALO 90 ablation catheter, Medtronic, Sunnyvale, Calif, USA). Generally, 2 applications of RFA are performed per site. Ablations are performed about 1 mm proximal to the dentate line (to prevent sensory injury to the anal mucosa) and restricted to a short length (<6 cm to the dentate line). The endoscope and device are removed for cleaning every 8 applications to preserve electrode surface effectiveness for other sites. The coagulum in treated areas is left on the mucosa and not scraped off to help promote hemostasis. There are no comparative studies or randomized trials evaluating the effectiveness of RFA for chronic radiation proctopathy.

In our systematic review, we found 3 case series with a total of 66 patients (Table 5).[53-55] The largest study consisted of 39 consecutive chronic radiation proctopathy patients with rectal bleeding who had failed prior medical prior therapy.[54] Rectal bleeding improved in all 39 patients (pre-RFA hemoglobin, 11.8 mg/dL; post-RFA hemoglobin, 13.5 g/dL) after a mean of 1.5 sessions and a 12- to 16-week time interval between treatment sessions. Mean follow-up of patients was 28 months (range, 7-53). There were no reported serious adverse events. In another case series of 17 patients with chronic radiation proctopathy and rectal bleeding who failed medical therapy, Dray et al[53] reported that RFA had an 88% success rate (15/17 patients) after a mean of 1.9 sessions and a 1-month time interval between treatment sessions. No serious adverse events were reported after 6 months of follow-up. In terms of RFA settings, most studies used an energy density of 12 to 15 J/cm^2 at a power density of 40 W/cm^2. A meta-analysis was not performed because of the limited number of studies.

Adverse events. No serious adverse events using RFA for chronic radiation proctopathy have been reported in the literature. However, mild anorectal pain can occur in up to 12% of sessions.[53-55]

Cryoablation

Cryoablation involves the noncontact application of carbon dioxide or liquid nitrogen to freeze cells and cause superficial ablation of rectal tissue. Its effect is mainly due to ischemic necrosis of the affected rectal mucosa, which can be immediate or delayed. Like APC and RFA, it has the same advantage of being able to treat a large surface area. No randomized trials or comparative studies have assessed the effectiveness of cryoablation for chronic radiation proctopathy.

However, 2 small case series showed improved rectal bleeding cessation for chronic radiation proctopathy (Table 5).[56,57] In a case series of 7 patients with rectal bleeding from chronic radiation proctopathy that was refractory to other endoscopic therapy (laser, thermal, or electrosurgical coagulation), Kantsevoy et al[57] reported a 100% clinical success with cryoablation using liquid nitrogen. The mean number of cryoablation sessions was 3.7, and the time interval between treatment sessions ranged from 2 to 3 days. No serious adverse events were

TABLE 5. Summary of studies using bipolar electrocoagulation, heater probe, radiofrequency ablation, and cryoablation for chronic radiation proctopathy

First author, year	Type of study	No. of patients	Gender (M/F)	Age (y)	Modality	Energy density (J/cm^2)	Power setting	No. of treatment sessions	Time interval between treatment sessions	Follow-up time (mo)	Endpoint	Efficacy	Serious adverse events
Bipolar electrocoagulation													
Castro Ruiz, 2013[49]	Case series	55	NR	51.2 (mean)		NA	NR	3	NR	NR	Bleeding cessation	55/55 (100%)	NR
Jensen, 1997[50]	Randomized trial	12	10/2	74.0 (mean)		NA	50 W	4 (median)	4-6 wk	12	Bleeding cessation	9/12 (75%)	0/12 (0%)
Lenz, 2011[29]	Randomized trial	15	8/7	64.4 (mean)		NA	50 W	2.9 (mean)	30 days	12	Telangiectasia eradication	14/15 (93.3%)	4/15 (26.7%)
Sharma, 2013*[51]	Randomized trial	14	NR	NR		NA	NR	4	NR	6	Bleeding cessation	11/14 (79%)	NR
Heater probe													
Jensen, 1997[50]	Randomized trial	9	8/1	76.0 (mean)		NA	10-15 J	4 (median)	4-6 wk	12	Bleeding cessation	6/9 (67%)	0
Fuentes, 1993[52]	Case series	8	NR	NR		NA	200-400 J	NR	NR	NR	Bleeding cessation	8/8 (100%)	0
Radiofrequency ablation													
Dray, 2014[53]	Case series	17	12/5	74.0 (mean)	Halo 90, 60	12-15	40 W	1.9 (mean)	1 mo	6	Bleeding cessation	15/17 (88%)	0
Rustagi, 2015[54]	Case series	39	39 men	73.0 (mean)	Halo 90	12	40 W	1.5 (mean)	12-16 wk	28 (mean)	Bleeding cessation	39/39 (100%)	0
Shahbaz, 2014*[55]	Case series	10	9/1	72.0 (mean)	Halo 90, 60	NR	NR	1.6 (mean)	NR	NR	Bleeding cessation	10/10 (100%)	0
Cryoablation													
Hou, 2011[56]	Case series	10	10 men	62.3 (mean)		NA	NR	1	NA	3.3 (mean)	RTD score improvement	7/10 (70%)	1/10 (10%)
Kantsevoy, 2003[57]	Case series	7	6/1	64.0 (mean)		NA	NR	3.7 (mean)	2-3 days	6	Bleeding cessation	7/7 (100%)	0

NR, Not reported; *NA*, not available; *RTD*, rectal telangiectasia density.
*Denotes abstracts.

reported in this study after 6 months of follow-up. In another case series of 10 patients with bleeding from chronic radiation proctopathy, 70% had clinical success after a single cryoablation session.[56] In addition, the radiation proctitis severity assessment scale, a composite of other radiation-related symptoms including diarrhea, urgency, rectal pain, tenesmus, rectal bleeding, and fecal incontinence, decreased by 51% after a single cryoablation session, from 27.7 to 13.6 (P = .009). No significant change was observed in hemoglobin. Mean follow-up time was 3.3 months. To date, both cryoablation systems reported above have been discontinued.[56,57] Currently, there have been no published data on new-generation cryoablation systems for chronic radiation proctopathy.

Adverse events. The overall serious adverse event rate is up to 10%, based on the 2 case studies included in our systematic review.[56,57] However, the single reported perforation from Hou et al[56] (1 of 10 patients in the study), which required a colectomy, was because of over-insufflation, likely caused by a failure of the decompression tube rather than cryotherapy itself.

Other therapies for chronic radiation proctopathy

Our systematic review only focused on endoscopic interventions for bleeding from chronic radiation proctopathy. We did not perform a systematic review on medical and surgical therapies for chronic radiation proctopathy; however, systematic reviews have summarized the effectiveness of medical therapies for chronic radiation proctopathy.[6,62] Additional data include randomized trials on medical treatment using oral metronidazole,[58] short-chain fatty acids,[59] formalin,[60,61] and sulfasalazine/5-aminosalicylic acids for chronic radiation proctopathy.[62] Other medical treatments used for radiation proctopathy,[62] some with mixed success, include steroids,[63] antioxidants,[64] sucralfate enemas,[65] and hyperbaric oxygen.[66,67] Surgical intervention is often the last therapeutic option for patients with chronic

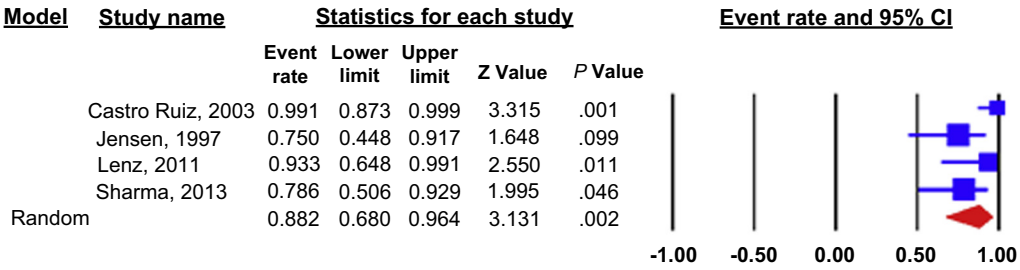

Figure 2. Forest plot of studies assessing clinical success of bipolar electrocoagulation for bleeding from chronic radiation proctopathy. *CI*, Confidence interval.

radiation proctopathy.[68] It is estimated that less than 10% of patients with chronic radiation proctopathy will ultimately require surgery.[69] Indications for surgical intervention include perforation, intractable bleeding or bleeding refractory to medical and/or endoscopic therapy, obstructing stricture, and fistula formation.[68] The decision on medical versus endoscopic management should be individualized based on patient and provider preferences, local resources, and expertise.

FUTURE DIRECTIONS

To provide better evidence-based recommendations for clinicians and patients, higher-quality, sufficiently powered comparative studies and controlled trials are needed on endoscopic therapies for chronic radiation proctopathy. In addition, there is an urgent need for a well-defined diagnostic criterion, a unified endoscopic grading system to better categorize radiation proctopathy, and clear, well-defined clinically relevant endpoints. Although we identified 2 scoring systems in the literature, further validation is required before implementation of these scoring systems in clinical practice.[18,53] Without these fundamental elements, future trials and comparative studies will not have a meaningful impact on this debilitating condition. Additional prospective studies on the safety and efficacy of the latest-generation cryoablation system for management of chronic radiation proctopathy should be pursued. Currently, there are no data on patient preferences for various treatment strategies, and studies carefully evaluating patient preferences are needed to help inform future guidelines. Finally, cost-effectiveness studies of endoscopic therapy compared with medical therapy should be addressed in future studies.

CONCLUSIONS

Chronic radiation proctopathy is a commonly observed late side effect of radiation therapy for cancers in the pelvic region, occurring within a year or several years after treatment. Although symptoms are often self-limited, some patients may require endoscopic management. Currently, the evidence for the effectiveness of endoscopic therapy for chronic radiation proctopathy is limited and hampered by a lack of controlled trials and uniform definitions for the disorder and outcomes. As a result, we were unable to evaluate the comparative effectiveness among different endoscopic modalities (eg, APC, bipolar electrocoagulation, heater probe, RFA, and cryoablation) for chronic radiation proctopathy. Despite this limitation, our systematic review of mostly case series and small prospective trials showed that APC, bipolar cautery, heater probe, and RFA were effective in the treatment of rectal bleeding from chronic radiation proctopathy. Choice of endoscopic modality may ultimately depend on availability, costs, and patient preference.

RECOMMENDATIONS

1. In patients with chronic radiation proctopathy, we suggest APC, bipolar electrocoagulation, heater probe, and RFA for treatment of bleeding from chronic radiation proctopathy. There is insufficient evidence to recommend a specific endoscopic modality over another for treatment of bleeding from chronic proctopathy.
2. In patients with chronic radiation proctopathy, we suggest against the use of 4% formalin compared with APC because of higher adverse event rates compared with APC for treatment of bleeding from chronic radiation proctopathy.
3. In patients with chronic radiation proctopathy, there is insufficient evidence for or against the use of the newer-generation cryoablation systems for treatment of bleeding from chronic radiation proctopathy.

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Abbreviations: APC, argon plasma coagulation; ASGE, American Society for Gastrointestinal Endoscopy; RFA, radiofrequency ablation..

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APPENDIX 1. SEARCH STRATEGY

Search strategy using Ovid Medline from 1946 to January 2017 and Embase 1988 to January 2017.

MeSH terms

((((((((("Argon plasma coagulation"[mh] OR "Argon plasma coagulation" OR "cautery" [mh] OR cautery OR "bipolar coagulation" OR Cryotherapy OR "Catheter Ablation"[mh] OR "Radio frequency ablation" OR "Radio-frequency ablation" OR "Hemostasis, Endoscopic"[Mesh] OR "endoscopic hemostasis" OR "endoscopic haemostasis" OR "Lasers, solid state"[mh] OR "solid state lasers" OR YAG laser OR neodymium:yttrium-aluminum-garnet OR Nd:YAG laser OR "Argon laser" OR BiCap OR "Potassium titanyl phosphate laser" OR KTP laser OR "Heater probe" OR "Bipolar cautery" OR Bipolor electrocautery OR "Bipolar electrocoagulation" OR ((BARRX OR HALO) AND ablation) OR Cryoablation))))) AND (("Radiation Injuries"[Mesh] OR "radiation injury" OR "radiation injuries") AND ("Proctocolitis"[Mesh] OR Proctocolitis OR Colitis OR Proctopathy OR Coloproctopathy)) OR ("radiation proctopathy" OR "radiation proctocolitis" OR "radiation proctopathy" OR "radiation telangiectasia")))))))

VIDEO LINKS

American Society for Gastrointestinal Endoscopy Video Tip of the Week: APC for radiation proctopathy: https://www.youtube.com/watch?v=wtrGLJkNchQ