Endoscopic management of chronic radiation proctitis

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Abstract
Chronic radiation proctopathy occurs in 5%-20% of patients following pelvic radiotherapy. Although many cases resolve spontaneously, some lead to chronic symptoms including diarrhea, tenesmus, urgency and persistent rectal bleeding with iron deficiency anemia requiring blood transfusions. Treatments for chronic radiation proctitis remain unsatisfactory and the basis of evidence for various therapies is generally insufficient. There are very few controlled or prospective trials, and comparisons between therapies are limited because of different evaluation methods. Medical treatments, including formalin, topical sucralfate, 5-amino salicylic acid enemas, and short chain fatty acids have been used with limited success. Surgical management is associated with high morbidity and mortality. Endoscopic therapy using modalities such as the heater probe, neodymium:yttrium-aluminium-garnet laser, potassium titanyl phosphate laser and bipolar electrocoagulation has been reported to be of some benefit, but with frequent complications. Argon plasma coagulation is touted to be the preferred endoscopic therapy due to its efficacy and safety profile. Newer methods of endoscopic ablation such as radiofrequency ablation and cryotherapy have been recently described which may afford broader areas of treatment per application, with lower rate of complications. This review will focus on endoscopic ablation therapies, including such newer modalities, for chronic radiation proctitis.

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Key words: Chronic; Radiation proctitis; Endoscopic; Argon plasma coagulation; Radiofrequency; Cryoablation

INTRODUCTION
Chronic radiation proctopathy (CRP) is a troublesome complication occurring in 5%-20% of patients following pelvic radiotherapy for carcinoma of the prostate, rectum, urinary bladder, cervix, uterus and testes[1-6]. Radiation-induced mucosal damage results in endothelial dysfunction, microvascular injury with intimal fibrosis, and fibrin thrombi of small arteries and arterioles leading to ischemia, fibrosis and the development of neovascular lesions[1,2]. CRP resolves spontaneously in many cases, but in some can lead to persistent rectal bleeding and iron deficiency anemia requiring blood transfusion[3]. Other symptoms of CRP include diarrhea, mucoid discharge, urgency, tenesmus, rectal pain and fecal incontinence. These symptoms interfere with daily activities and have an adverse effect on quality of life[4]. Treatment for CRP remains unsatisfactory. Medical measures, including formalin application[5], topical sucralfate[6], 5-amino salicylic acid enemas[7], short chain fatty acids[8] and antioxidants...
CONTACT PROBE THERAPY: HEATER AND BIPOLAR PROBE

The heater probe has a teflon-coated heating element at its tip that delivers standardized energy over set times. Bipolar electrocautery probe has a pair of electrodes at its tip through which current is passed using the tissue for conduction. Both devices are contact probes, making them useful for directed therapy in the setting of active bleeding. The disadvantage is char formation on the tip of the probe, leading to decreased treatment efficiency and requiring repeated cleaning. Fuentes et al treated 8 patients with the heater probe for rectal bleeding, which required one to four treatment sessions for complete cessation or significant reduction in bleeding. In a randomized prospective trial by Jensen et al, a total of 21 patients were treated either by a heater probe (n = 9) or a bipolar electrocoagulation probe (n = 12). A mean of four sessions were required for either probe. In the 12 mo of endoscopic treatment vs 12 mo medical therapy, the severe bleeding episodes diminished significantly for the bipolar probe (75% vs 33%) and heater probe (67% vs 11%). No side effects were reported in any of the studies using these modalities (Table 1).

LASER THERAPY

Nd:YAG

Nd:YAG laser was one of the first endoscopic laser modalities used in the treatment of CRP. Leuchter et al reported successful treatment of rectal hemorrhage in a patient after four applications. The laser uses a 1.06 µm wavelength and penetrates to a depth of up to 5 mm. Nd:YAG laser has a low affinity for hemoglobin and H2O but is well absorbed by tissue protein, thus making it ideal for deeper vessel coagulation. Initially, a setting of 40 W and pulse duration of 1/2 s maximum is used with the tip at approximately less than 1 cm from the mucosal surface. The desired effect in treating telangiectasias is attained with the formation of white coagulum. The study by Barbaczos et al involved nine patients who underwent a mean of three treatments. There were no complications, and bleeding was decreased to occasional spotting. Venutucci et al also reported successful treatment in nine patients. The median number of treatments required per patient was three to achieve cessation of bleeding in four patients and occasional spotting in four others. One patient still required transfusions at completion of the study. Transmural necrosis, fibrosis, stricture formation and recto-vaginal fistula are some of the complications reported with use of Nd:YAG. Nd:YAG use for CRP has declined because of its cost, the need to aim directly at telangiectasias, and the possibility of severe endoscopic damage if the laser strikes the endoscope in retroflexion (Table 2).

Potassium titanyl phosphate

The KTP laser uses the beam from the Nd:YAG laser that is passed through a KTP crystal, reducing the wavelength by half (532 nm). At this wavelength, the energy is absorbed by hemoglobin and the depth of penetration is more shallow (1-2 mm) compared to Nd:YAG. This affinity for hemoglobin permits selective coagulation, thus making it quite useful in the treatment of superficial vascular lesions. The use of KTP for CRP has been limited. Taylor et al treated 26 patients with bleeding secondary...
to CRP using 4-10 W and a median of two sessions. They reported a symptomatic improvement in 65% patients, while there was no change in seven (30%) and there was an increase in hematocrit in one (5%). No perforations or fistula formation were reported in the study.

**Argon laser**

The argon laser is functionally similar to KTP with similar wavelength, resulting in tissue heat penetration of 1-2 mm depth, and is also useful in superficial blood vessel photocoagulation. O’Connor treated five patients using the argon laser at 1.5 W and reported cessation of bleeding after two to four treatment sessions with no complications. Buchi and Dixon treated three patients successfully, with only one patient reporting cramps. Similarly, Taylor treated three patients successfully, with only one patient reporting cramps. Similarly, Taylor treated three patients successfully, with only one patient reporting cramps. Similarly, Taylor treated three patients successfully, with only one patient reporting cramps.

**ARGON PLASMA COAGULATION**

Laser therapy for hemorrhagic CRP was largely supplanted by argon plasma coagulation (APC), which is less expensive, easier, safer and more widely available. This involves the application of bipolar diathermy current using inert argon gas as a conducting medium, delivered via a through-the-scope catheter. Unlike traditional bipolar devices, the current jumps from the probe to the target lesion, with the arc being broken once the tissue is desiccated. The theoretical advantage is a uniform, more predictable and limited depth of coagulation (0.5-3 mm), to minimize the risks of perforation, stenosis and fistulization. APC can be applied axially and radially, allowing tangential coagulation of lesions around rectal bends. Also, the APC generator is mobile and can be used quickly and at any place or time. Given all these benefits, APC has rapidly become the preferred, first-line endoscopic therapy for hemorrhagic CRP (Table 3).

Most studies on the use of APC in the management of CRP have demonstrated benefit (Table 3). APC ameliorates rectal bleeding associated with mild to moderate hemorrhagic CRP in 80%-90% of cases, and improves symptoms of diarrhea, urgency and tenesmus in 60%-75% of cases. Ten studies also reported an increase in the mean hemoglobin levels after APC in almost all patients after the treatment, suggesting the effective control of rectal bleeding. Cumulative average increase in mean hemoglobin levels is around 2.26 gm% (range, 1.1-3.8 gm%). Relief of blood transfusion dependency has also been reported in almost all patients treated with APC (57 of 60 patients, 95%) in one series (Table 3).

However, APC has inherent limitations especially in very severe, extensive CRP, e.g., with greater than half of the rectal surface area involved or with fresh surface bleeding. More diffuse lesions usually require repeated applications per session and multiple treatment sessions (ranging from one to five sessions). A few studies report up to 8 sessions needed to achieve complete resolution of symptoms, endoscopic disappearance of all telangiectasias, and complete cessation of bleeding. The mean number of sessions per patient reported varies from 1 to 3.6 with a calculated overall cumulative mean of 2.13 sessions per patient (calculated median: 2) (Table 3). Mean interval between sessions usually ranges from 4 to 8 wk. Follow-up ranges from 1 to 48 mo with a mean of 3-31 mo across different studies (calculated overall mean: 15 mo). Recurrent proctopathy has been reported

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**Table 1** Literature on contact probe therapy use in chronic radiation proctopathy

| Author(s) | Modality        | n  | Power settings | Mean no. of sessions | Response rate | Duration of study | Side effects |
|-----------|-----------------|----|----------------|----------------------|---------------|-------------------|-------------|
| Jensen et al. 1997 | Heater probe     | 12 | 4 (mean)       | 10-15 W, 1 s pulses | 12/12 (100%)  | 24/12            | None        |
| Fuentes et al. 1993 | Heater probe   | 8  | 1-4            | 20 J/pulse          | 8/8 (100%)    | N/A              | None        |
| Jensen et al. 1997 | Bipolar         | 9  | 4 (mean)       | 10-15 J             | 9/9 (100%)    | 24/12            | None        |
| Hauk et al. 1996 | Bipolar         | 8  | 2.5-15 W or 11-25 W | 8/8 (100%)      | 4/12          | None              |
| Marnouy et al. 1991 | Bipolar    | 4  | Setting 5, 2 s pulses | 4/4 (100%)     | 9/12          | None              |

N/A: Not available.

**Table 2** Literature on neodymium:yttrium-aluminium-garnet laser therapy use in chronic radiation proctopathy

| Author(s) | n  | Power settings | Mean no. of sessions | Response rate | Duration (mo) | Side effects |
|-----------|----|----------------|----------------------|---------------|---------------|-------------|
| Ventrucci et al. 2001 | 9  | 4 W           | 3                    | 4/9 (44% CR), 4/9 (44% PR) | N/A          | None        |
| Taylor et al. 2000 | 23 | 4-10 W        |                      | 15/23 (65%)   | 6             | 2 rectal ulcers |
| Barbatoz et al. 1996 | 9  | 20-30 W       | 3                    | 6/9 (66% PR)  | 24            | None        |
| Chapuis et al. 1996 | 34 | 40 W          |                      | 30/34 (88%)   | 6-64          | 4 mucous discharge, 1 acute prostatitis, 1 rectal stricture |
| Lucaroti et al. 1991 | 5  | 80 W          |                      | 5/5 (100%)    | 18            | NA          |
| Jacobs 1989 | 2  | NA            |                      | 2/2 (100%)    | 12            | NA          |
| Alexander et al. 1988 | 8  | 80-90 W       |                      | 6/8 (75%)     | 21            | 3 ileus, 1 abdominal pain |
| Alkuist et al. 1986 | 4  | 30-40 W       | 4                    | 2/4 (50% CR)  | 12            | 1 tenesmus |
| Leuchter et al. 1982 | 1  | 60 W          | 4                    | 1/1 (100% CR) | 24            | None        |

CR: Complete remission; PR: Partial remission; NA: Not available.
### Table 3: Literature on argon plasma coagulation therapy use in chronic radiation proctopathy

| Study Ref. | n | Mean age (yr) | Settings - flow rate - power | Mean No. of sessions per patient | Response rate | Improvement in anemia (% patients), mean increase in Hgb (gm%) | Relief of transfusion dependency | % requiring transfusion | Complications/Side effects | % requiring trans-fusion |
|------------|---|---------------|------------------------------|---------------------------------|--------------|------------------------------------------------------------|-----------------------------|----------------------|--------------------------|------------------------|
| Swan et al, 2010 | 50 | 72.1 (51-87) | 1.4-2 L/min, 50 W | 1.36 (1-3) | 96% | 1.9 gm% mean increase | 20.6 (6-48) | Short-term: 17 (34%) patients (proctalgia in 13, rectal mucous discharge in 4, incontinence in 1); long-term: 2 (2%) asymptomatic rectal strictures | N/A | None |
| Karamanolis et al, 2009 | 17 | 73.4 (65-85) | 2.0 L/min, 40 W | 2 (1-8) | Mild (100%), severe (79%), total (89%) | N/A | 7/9 | 17.9 (6-33) | N/A | None |
| Torno et al, 2009 | 22 | 73.5 (65-67) | 2.58 (1-7), median-2 | 100% | N/A | N/A | N/A | N/A | N/A | None |
| Al-Allaf et al, 2008 | 14 | 74.7 (65-50) | 1.2-2 L/min, 45-50 W | 1.78 | 78.5% | 2 gm% mean increase | N/A | 3 | 2/14 (33.3%) mild: N/A |
| Latorre et al, 2008 | 38 | 70.9 | 3.6 ± 2.7 | | | | | | |
| Dees et al, 2008 | 48 | 2 L/min, 50 W | Median-2 | 98% | | | | | |
| Ben-Sousan et al, 2004 | 27 | 73.1 (53-86) | 1 L/min, 40 W | 2.66 (1-7) | 92% | | | | |
| Higueras et al, 2004 | 10 | 1.5-2.0 L/min, 60 W | 1.9 (1-4), median-1 | 100% | 1.5-1.9 gm% mean increase | 1/1 | 3.11 (10-45) | N/A | None |
| Sebastian et al, 2004 | 25 | 69 (53-77) | 1.5 L/min, 30 W (25-40 W) | 2.4 gm% mean increase | | | | | |
| Urban et al, 2004 | 8 | 72.3 | 1-4 | | | | | | |
| Ravizza et al, 2003 | 27 | 72 (62-83) | 2 L/min + 60 W (n = 17) | 2 (1-5) | 85% marked improvement, 10/27 only had minor bleeding, 48% Complete resolution | 3.2 g/dL mean increase | 6/6 (100%) | 11.5 (1-24) | Short term: 2/27 (7%), 1 transient anal/rectal pain, 1 fever; long-term: 1/4 (25%)-asymptomatic rectal ulcers |
| Ghoorghe et al, 2003 | 42 | 60 W (23), 50 W (19) | | 1.34, 1.9 | | | | | |
| Canard et al, 2003 | 30 | 70.7 (58-85) | 0.8-2 L/min, 50-80 W | 2.3 (1-5) | (87%) | | | | |
| Venkatesh et al, 2002 | 40 | 64.8-1.5 L/min, 40-60 W | Mean-1.35, median-1.2 (1-2) | 97.5% | - | 20/21 (95.2%) | NR-3.30 | 21/40 (52.5%) | 1-urinary retention, 2-fever requiring antibiotics |
| Talib et al, 2001 | 11 | 73 (54-86) | 0.8-2 L/min, 50 W | 3.2 (1-5) | 82% CR, 18% PR | 3.8 gm% mean increase | 7/7 (100%) | 19 (7-30) | 17% |
| Tjandra et al, 2001 | 12 | 60 W | 2 (1-3) | 50% CR, 50% PR, 83% Signi | 1.1 gm% mean increase | 4/4 (100%) | 11 (4-17) | 4/12 (33%) | None |
| Smith et al, 2001 | 7 | 60 W (18.75%) | 1 L/min, 60 W | | 71% CR, | 29% PR | 1.8 gm% mean increase | 6 (3/12 25%), 2-chronic rectal ulcerations, 1-asymptomatic rectal stenosis | | |
| Balachon et al, 2000 | 12 | 70.3 (62-80) | 1 L/min, 50 W | 2.8 (2-8) | 83% PR | 4/4 (100%) | 11 (4-17) | 4/12 (33%) | None |
| Kaissis et al, 2000 | 16 | 73.5 (62-80) | 0.6 L/min, 40 W | Mean-3.7, (2-8) | 44% CR, | 10.7 (8-28) | No | | |
| Tam et al, 2000 | 15 | 70.7 (58-85) | 2 L/min, 60 W | 2 (1-4) | 100% | 2.5 gm% mean increase | | 3/3 (100%) | 3/15 (20%) | None |
| Silva et al, 1999 | 28 | 65 (42-77) | 1.5 L/min, 50 W | 2.9 (1-8) | 93% | 1.2 gm% mean increase | - | 10 (1-15) | 15/28 (53%) |
| Farzin et al, 1999 | 7 | 60 W (42-77) | 50 W | 2 (2-4) | 100% | | | | |
| Churkan et al, 1999 | 12 | 60 W | 1 | 92% | | | | | |
| Villavicencio et al, 2002 | 21 | 72.6 (38-86) | 1.2-2.0 L/min, 40-50 W | 1.7 median (1-4) | 100% | | | | |
| Rotondano et al, 2003 | 24 | 8.1 L/min, 40 W | Median-2 | 100% | | | | | |
| Zinicola et al, 2003 | 14 | 72.6 (65-85) | 2 L/min, 65 W | 2 (1-4) | 86% | | | | |
to respond to additional rounds of APC therapy. Patients on anticoagulants or aspirin demonstrate higher recurrence. Kaassis et al. found that patients who were receiving anticoagulation therapy may require more APC sessions, but can achieve an equivalent clinical response as those who are not on anticoagulation. Rectosigmoid lesions are also more difficult to treat due to the tortuosity that often accompanies radiation injury in this region. When rectal lesions are very distant from the anus, application of APC with a rigid probe through an operating sigmoidoscope may be easier than through a flexible endoscope. Lesions located immediately above the dentate line in the upper part of the anal canal are also difficult to treat. These may require retroflexion of the scope with higher risk of rectal scarring, limited mobility of the endoscope, and greater patient discomfort. One technique described by Coriat et al. using a transparent cap attached to the tip of the colonoscope, allowed better visualization of low rectal lesions and of the upper part of the anal canal without retroflexion and proper distance for effective and safe APC delivery. Notwithstanding, APC may be avoided in the presence of radiation-induced rectal strictures and fistulae, which may worsen as the treated area heals.

Overall, the reported complication rate with APC has been variable (Table 3). Canard et al. reported an overall morbidity of 47%: post-treatment pain in 20% and severe complications in 3 (10%), including a patient with severe bleeding, extensive necrosis of lower part of the rectum, and perforation. Alfadlli et al. and Swan et al. reported complications in 30%-35%. On the other hand, the experiences of Villavincencio et al. and Swan et al. were better, with a 19% incidence of both short-term (such as tenesmus, anismus) and long-term (including diarrhea, rectal pain) complications. The commonest procedure-related complication reported is anal or rectal pain with or without tenesmus, which is most likely to occur following treatment near the dentate line, and usually resolves spontaneously within few days or with standard analgesics. Abdominal bloating and cramping, and vagal symptoms related to colonic distension have also been reported. One potential drawback of using APC is the possibility of excessive luminal distention from the rapid instillation of argon gas that occurs during treatment. It is recommended that, when possible, a two-channel endoscope should be used so that the insufflated argon gas can be removed periodically during the procedure. Several authors have reported colonic explosion [1 of 56 (1.8%) with or without perforation (Table 3) when the bowel has not been formally cleansed, and adequate colonic lavage is therefore a mandatory requirement. Rare complications reported include arteriovenous fistula, urinary retention and necrosis of lower part of the rectum. Although life-threatening gas embolism has been reported during bronchoscopic application of APC, no such complication has been reported during gastrointestinal endoscopic application.

Rectal ulcers are common following APC treatment. Severe ulceration may result in “painting” of the rectal wall. Therefore, brief pulse treatment of targeted lesions is recommended. Ravizza et al. reported asymptomatic rectal ulcers in 14 (52%) of 27 patients, a frequency that is relatively high in comparison with the reported overall frequency of about 3%-16% (Table 3) in other series, despite similar gas flow rate and power settings compared to the other studies. Furthermore, this data may underestimate the true frequency of rectal ulcer, as 41% of the patients in this study did not undergo endoscopy after the last APC session. However, no strictures were observed after ulcer healing. Rectal ulcers developing during APC can be considered a consequence of thermal injury to already damaged and vascularly compromised tissue that is thus more fragile and has poorer healing. Incidence of ulcers may be affected by the flow rate of the argon gas and power settings, the method of application, the interval between sessions, and the number of sessions subsequent to ulcer development which may delay ulcer healing due to repeated thermal injury. The fact that rectal ulcers are not clinically troublesome means they should not be considered an absolute contraindication to APC, nor do they necessarily require any additional endoscopic follow-up.

Compared to ulcers, the occurrence of strictures is less common. The frequency of this complication varies among different studies, many studies describing no occurrence of rectal strictures while few studies reporting such complication in 2%-13% (Table 3). A review of literature by Ravizza et al. reported 9 cases of asymptomatic rectal strictures in 207 treated patients, with an overall frequency of 4.3%. However, given the fact that most of the rectal strictures are asymptomatic, their true incidence is difficult to estimate and theoretically would be higher than reported by several studies.

The studies involving APC are not uniform in methodology. The power settings range from 30 to 60 W (median 40-50 W), with an argon flow rate from 0.8 to 2 L/min (median 1.5-2 L/min) (Table 3). Lower power settings have been subscribed for lower complication rate and decreased number of treatment sessions required for complete coagulation, with almost all complications occurring at power settings above 45 W. Duration of burn and power settings have also been correlated with depth of injury to the muscularis propria in swine colon. Thus lower power settings appear to cause less injury while coagulating just as well as at higher settings. Unfortunately, most of the studies do not report the success of individual settings. Only few studies have compared APC at different settings. One small study of 42 patients compared 50 and 60 W therapies, but reported no statistical difference between the two. Ravizza et al. found a higher rate of rectal ulceration with higher settings; 59% with flow of 3 L/min and a power of 60 W compared to 40% with a 2 L/min flow and a power of 40 W, albeit without statistical significance (P = 0.4) in the limited study.

No prospective comparative trials of the APC with other endoscopically directed treatment modalities exist, nor is there any experience on the role of adjuvant medical therapy such as the use of steroids, sulcrate or 5-aminosalicylic acid enemas between APC sessions. Most importantly, there are no control or crossover studies.
However, in many of the studies involving APC, most of the patients had unsuccessful results with medical therapy before undergoing APC. For example, in the study by Ravizza et al.\[^{11}\], 17 of their 27 patients had been treated unsuccessfully with corticosteroid or salicylate enemas. Tjandra et al.\[^{12}\] also found APC to be effective in 11 patients with CRP refractory to formalin therapy. Similarly in the study by Villavicencio et al.\[^{13}\], 12 of their 21 patients had been treated unsuccessfully with various pharmacologic agents including oral and rectal mesalamine, and rectal corticosteroids. Other forms of endoscopic treatment (laser photocoagulation, multicolor coagulation) had been performed in 5 of their patients, all failed in achieving control of bleeding\[^{14}\]. In a study by Zinicola et al.\[^{15}\], 6 (42.8%) patients had previously failed treatment with steroid enemas or 5-aminosalicylic acid enemas. In a recent study by Swan et al.\[^{16}\], 16 patients who failed in previous treatments for CRP all responded to endoscopic APC therapy. Alfadhli et al.\[^{17}\] retrospectively compared the APC with topical formalin, and found APC to be more effective (79% vs 27% responders) and safer (14.3% vs 81.8% adverse effects) than topical formalin in controlling hemorrhage. The rate of single-session APC responders (63.6%) was almost double that of the formalin-treated group (33.3%)\[^{18}\].

### RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) with the BARRx Halo90 system has achieved superficial and broad fields of ablation in the esophagus\[^{19}\] suggesting that similar benefits could be achieved in the colon and rectum. Zhou et al.\[^{20}\] have reported successful use of RFA with the BARRx Halo90 system in treating three patients with lower gastrointestinal bleeding from CRP, including two who failed in conventional therapy. In all cases, the procedure was well tolerated and hemostasis was effectively achieved after 1 or 2 RFA sessions. Re-epithelialization by neosquamous mucosa was observed over areas of prior hemorrhage above the prior dentate line. No strictureing or ulceration was seen on follow-up up to 19 mo after RFA treatment. In this report, real-time in vivo endoscopic optical coherence tomography (EOCT) was also used to assess the treatment efficacy. EOCT could visualize epithelialization and subsurface tissue microvasculature before and after treatment, demonstrating its potential for follow-up assessment of endoscopic therapies and directing areas for retreatment, without the need for excisional biopsy. This is particularly important for patients with radiation proctitis since biopsy is relatively contraindicated due to the high risk of rel bleeding.

Several benefits of RFA have been found compared with other endoscopic treatments for radiation proctitis. These include squamous re-epithelialization seen after RFA with prevention of rel bleeding and the relative lack of strictureting and ulceration that is seen often after other thermal ablative procedures. The tightly spaced bipolar array of the RFA catheter limits the radiofrequency energy penetration, restricting the RFA treatment to the superficial mucosa, thereby avoiding deep tissue injury in relatively ischemic mucosa and resulting in post-treatment ulceration and structuring, as commonly noted following conventional endoscopic therapies. Finally, RFA allows much broader areas of tissue to be treated simultaneously compared to the point-by-point approach required with heater or bipolar probes\[^{21}\] or APC\[^{22}\]. As with APC, the unit is mobile and can be used in different rooms of an endoscopic suite. The BARRs unit also delivers a consistent amount of energy to the surface using well-defined and reproducible ramp-up of energy. This minimizes the possibility of operator-dependence and over-treatment that may lead to perforations or ulcerations.

Nikfarjam et al.\[^{23}\] recently reported another case with extensive CRP that had continued bleeding despite APC. The HALO90 radiofrequency system was used for treating regions of proctitis at an energy density of 12 J/cm\(^2\). At monthly intervals, over 3 mo, RFA was performed with a mean of 7 regions ablated at a time. The mean treatment time was 29 min. There was no significant bleeding after the first treatment session. The patient was symptom free at 6 mo follow-up with minimal evidence of residual mucosal abnormalities.

### CRYOABLATION

Cryoablation, similar to APC, is a noncontact method of therapeutic tissue destruction via application of extreme cold temperatures to a targeted area. Cryoablation has the benefit of uniform treatment of larger surface areas and case of targeted application. Cryoablation works through immediate and delayed effects. Delayed effects are related to induction of ischemic necrosis.

Kantsevoy et al.\[^{24}\] reported the successful use of experimental endoscopic cryotherapy in patients with radiation proctitis, as a part of a pilot study that was conducted to evaluate the safety and efficacy of endoscopic cryotherapy for bleeding mucosal vascular lesions. They used a Prototype II device to spray nitrous oxide through the accessory channel of an upper endoscope\[^{25}\]. Complete cessation of bleeding was achieved in all 7 (100%) patients who underwent cryoablation therapy for radiation proctitis. A major advantage of the cryotheraphy technique identified was the ability to treat large areas of mucosa relatively quickly. The only adverse effect reported was transient abdominal pain with spontaneous resolution in one out of a total of 26 patients treated for various gastrointestinal mucosal bleeding lesions.

Shaib et al.\[^{26}\] reported the first case of mucosal healing and symptomatic resolution of radiation proctitis using low-pressure cryoablation (CryoSpray, CSA Medical) in a patient who previously did not respond to medical therapy with steroid suppositories. Cryoablation was performed using a liquid nitrogen spray injected through the cryoablation catheter passed through an endoscopic channel. A total of four 10-s applications were used for each area of proctitis. During cryoablation, a decompression tube was placed in the rectum to prevent over-insufflation. No adverse effects after cryoablation were seen. Hemoglobin was reported to increase from 9.4 g/dL to 11.7 g/dL over the 15-wk follow-up period with
sigmoidoscopic resolution.

Battish et al.\textsuperscript{67} also reported similar results in small case series of 2 patients with established radiation proctitis who underwent cryoablation using liquid nitrogen (CryoSpray). Each patient underwent 4 applications of 10 s each with complete resolution of mucosal bleeding and telangiectasias on follow-up endoscopy. The only post-procedure adverse effect reported was transient abdominal distention in one patient.

Most recently, Hou et al.\textsuperscript{68} reported a prospective case series of 10 patients with hemorrhagic CRP with a mean follow-up of 3.3 mo. All patients underwent a single endoscopic session of cryotherapy, consisting of three 5-s applications per involved area of mucosa, performed with a 9F cryoablation catheter (formerly CryMed, now CSA Medical). Endoscopic improvement was reported in 70% of patients, with an overall 37% decrease in rectal telangiectasia density from a mean of 2.7 to 1.7 ($P = 0.02$). Symptomatic improvement was observed in 80% of patients with an overall 51% reduction in Radiation Proctitis Severity Assessment Scale score from a mean of 27.7 to 13.6 ($P = 0.009$). Severe complication included one (10%) patient with cecal perforation secondary to over-inflation likely caused by a failure of the decompression tube. Subsequently, the protocol was adapted to reduce treatment duration and perform full colonoscopy after treatment for colonic decompression. One case (10%) of rectal ulcer was also reported\textsuperscript{68}.

Reports using cryoablation for CRP remain experimental and anecdotal. These early case reports support the use of cryoablation therapy in management of CRP. However, there has been no prospective study comparing cryoablation with other treatment modalities such as APC, with regards to efficacy, side effects and durability of results. Larger studies or case series are required to confirm the utility or superiority of cryoablation.

The current commercially available cryotherapy apparatus is less mobile and somewhat more cumbersome than most APC and the BARRX units, and requires maintaining a supply of liquid nitrogen which lasts approximately 2 wk in the current holding tank. Thus treatments for incidental lesions, particularly in a lower volume endoscopy unit, may be more difficult. In our view, a major advantage of cryotherapy over the other heat-generating ablative methods is that colonic lavage may be necessary, but the possibility of gas ignition is not necessary. However, drawing from the animal studies, the depth of tissue destruction may be deeper by CSA cryotherapy than that achieved by BARRx radiofrequency ablation, and it is unclear whether this could lead to greater strictures, abscess and fistulas, or whether cryotherapy is inherently less prone to such complications. Moreover, the rapidly expanding gas would require adequate venting which may be more difficult for lesions higher in the sigmoid colon.

CONCLUSION

Endoscopic therapies have become the treatment of choice in patients with troublesome bleeding due to CRP, and may be used in conjunction with medical therapies. The ability to safely treat these patients in an outpatient setting is extremely attractive. Endoscopic therapy has proven successful in stopping bleeding from CRP, in addition to providing symptomatic relief by reducing urgency, tenesmus, and the frequency of hematochezia and transfusion requirements. Initially, endoscopists had used the heater and bipolar probes, then the neodymium/yttrium aluminum garnet (Nd:YAG) and potassium titanyl phosphate lasers, which were each effective. Formalin administration through a rigid scope also proved effective. The use of APC by endoscopy has become an attractive treatment option, because it is a noncontact approach that is efficient, effective, relatively safe and well tolerated.

While focal ablative tools such as lasers, contact probes and APC may be helpful when bleeding occurs from limited number of identifiable ectatic vessels, a larger field of arteriovenous malformations (AVMs) or oozing may be more difficult to control. Moreover, poor healing and subsequent ulcerations can exacerbate bleeding in this CRP field, which is vascularly compromised. Therefore methods allowing for broader field of treatment such as formalin instillation, or the newer methods of RFA and cryotherapy may be theoretically advantageous in this setting. In particular, the unexpected finding of neosquamous epithelialization with RFA may have further advantages in preventing rebleed.

Future comparison of these treatment modalities would be enhanced using the uniquely-suited EOCT as an imaging tool, since this allows broad areas of scan with subsurface near-microscopic visualization for vessel features and density.

Present evidence for endoscopic therapy of CRP remains largely anecdotal, and future studies to demonstrate efficacy need to adopt a standard scoring system for CRP. Denton et al.\textsuperscript{9,10} suggested possible scoring systems and outcome measures (including quality-of-life scores) that seem sensible in this disease. Adaption of such scoring system may allow better comparison of different studies and different modes of treatment. Moreover, bleeding from CRP often resolves spontaneously, and there needs to be larger randomized controlled studies for the treatment of CRP. Given such limitations and differences in availability of equipment and expertise, it is difficult to recommend a truly evidence-based algorithm for management of CRP. However, we recommend a trial of medical therapy such as sucralfate enemas with oral metronidazole for mild cases. Severe cases, particularly hemorrhagic CRP and those refractory to medical treatment, should be promptly offered endoscopic therapy. Currently, APC is the preferred first-line endoscopic modality given the vast experience and availability. Refractory cases should be referred to centers for hyperbaric oxygen therapy or centers performing newer endoscopic therapies such as radiofrequency and cryoablation, which may become the standard of care in the future particularly for more extensive lesions.

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