REVIEW

Endoscopic management of chronic radiation proctitis

Tarun Rustagi, Hiroshi Mashimo

Tarun Rustagi, Department of Internal Medicine, University of Connecticut, Farmington, CT 06030, United States
Hiroshi Mashimo, Gastroenterology Section 111, VA Boston Healthcare System, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02130, United States
Author contributions: Rustagi T and Mashimo H contributed equally to this work and wrote the paper with final editing and approval.
Correspondence to: Hiroshi Mashimo, MD, PhD, Gastroenterology Section 111, VA Boston Healthcare System, Brigham and Women's Hospital, Harvard Medical School, 150 South Huntington Ave., Boston, MA 02130,
United States. hmashimo@hms.harvard.edu
Telephone: +1-857-2035640 Fax: +1-857-2035666
Received: January 19, 2011   Revised: May 14, 2011
Accepted: May 21, 2011
Published online: November 7, 2011

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 compli-cations. This review will focus on endoscopic ablation therapies, including such newer modalities, for chronic radiation proctitis.

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

such as vitamin E[9] and pentoxifylline[10] have been used with limited success. Surgical management is associated with high morbidity and mortality[11].

The basis of evidence for the therapy of CRP is generally insufficient. There are very few high-quality trials and comparisons between therapies are limited because of different evaluation methods. Most data are from case series of a single treatment from a single center. Therefore, a degree of pragmatism needs to be shown on the basis of these data and local availability of therapy. Sucralfate enemas seem to be the best available "medical" therapy and are safe and well tolerated. Additional use of oral metronidazole may enhance this effect[12]. Steroid enemas may have some effect, but are less well tolerated and probably have lower efficacy. Formalin therapy is effective in up to 48% of patients with CRP[13,14]. However, high rates of complications have been reported including rectal pain, incontinence, diarrhea, formalin-induced colitis, anal and rectal strictures, rectal ulcerations, and rectal perforation[13,14]. Also, the technique of application, concentration of formalin and the success rates reported in different studies highly vary[15]. The duration of effect based largely on anecdotal reports remains unclear, but appears to be around 3 mo[15]. Another described therapeutic modality is hyperbaric oxygen therapy, which is purported to have an angiogenic effect and stimulate collagen formation and re-epithelialization[16]. Aural barotrauma is the most common side effect reported, although it appears to be largely transient and minor[15,17]. The equipment needed is expensive and not readily available. Thus, at the present time, it is not a practical means of treating CRP outside of specialized centers and is usually reserved for cases refractory to more readily available forms of therapy.

The goal of endoscopic treatments of CRP is to achieve control of bleeding. Attaining this goal improves the patient's quality of life by reducing the need for iron replacement, blood transfusion and hospital admissions, resolving symptoms of anemia, and symptoms of hematochezia. Endoscopic therapy using modalities such as the heater probe[18], neodymium:yttrium-aluminium-garnet (Nd:YAG) laser[19,20], potassium titanyl phosphate (KTP) laser[21] and bipolar electrocoagulation[22] has been reported to be of some benefit, but at the expense of a high level of complications[23]. Of ablative therapies, thermal methods seem to be effective and safe. Simple heater probe treatment or argon plasma coagulation (APC) is the preferred method for their better safety profile. Intra-rectal formalin seems to be effective, but possibly has a higher rate of complications[14]. Newer methods of endoscopic ablation such as radiofrequency ablation and cryotherapy have been recently described which may afford broader areas of treatment per application. This review shall focus on endoscopic ablation therapies used in management of CRP.

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[24]. 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*[25] 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*[18], 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*[26] reported successful treatment of rectal hemorrhage in a patient after four applications. The laser uses a 1.06 nm wavelength and penetrates to a depth of up to 5 mm[27]. Nd:YAG laser has a low affinity for hemoglobin and H_2O but is well absorbed by tissue protein, thus making it ideal for deeper vessel coagulation[28]. 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 Barbatzos *et al*[20] involved nine patients who underwent a mean of three treatments. There were no complications, and bleeding was decreased to occasional spotting. Ventrucci *et al*[29] 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)[30]. 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*[21] treated 26 patients with bleeding secondary

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

Authors	Modality	*n*	No. of treatment	Power settings	Response rate	Duration of study	Side effects
Jensen et al[18], 1997	Heater probe	12	4 (mean)	10-15 W, 1 s pulses	12/12 (100%)	24/12	None
Fuentes et al[25], 1993	Heater probe	8	1-4	20 J/pulse	8/8 (100%)	N/A	None
Jensen et al[18], 1997	Bipolar	9	4 (mean)	10-15 J	9/9 (100%)	24/12	None
Haulk et al[69], 1996	Bipolar	8		2-5 W or 11-25 W	8/8 (100%)	4/12	None
Mannoury et al[22],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	*n*	Power settings	Mean no. of sessions	Response rate	Duration (mo)	Side effects
Ventrucci et al[29], 2001	9		3	4/9 (44% CR), 4/9 (44% PR)	N/A	None
Taylor et al[21], 2000	23	4-10 W		15/23 (65%)	6	2 rectal ulcers
Barbatzos et al[20], 1996	9	20-30 W	3	6/9 (66% PR)	24	None
Chapuis et al[70], 1996	34	40 W		30/34 (88%)	6-64	4 mucous discharge, 1 acute prostatitis, 1 rectal stricture
Lucarotti et al[11], 1991	5	80 W		5/5 (100%)	18	NA
Jacobs[71], 1989	2	NA		2/2 (100%)	12	NA
Alexander et al[72], 1988	8	80-90 W		6/8 (75%)	21	3 ileus, 1 abdominal pain
Alqhuist et al[73], 1986	4	30-40 W		2/4 (50% CR)	12	1 tenesmus
Leuchter et al[26], 1982	1	60 W	4	1/1 (100% CR)	24	None

CR: Complete remission; PR: Partial remission; NA: Not available.

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 hematochezia 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'Conner[31] 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[32] treated three patients successfully, with only one patient reporting cramps. Similarly, Taylor et al[33] reported control of bleeding achieved after a median of three sessions in 14 patients. Power was set between 3.5 and 8 W with a flow rate of 1.5-2.5 mL/s and no complication was encountered.

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)[34], to minimize the risks of perforation, stenosis and fistulization. APC can be applied axially and radially, al-

lowing tangential coagulation of lesions around rectal bends[35-37]. Also, the APC generator is mobile and can be used quickly and at any place or time[35-37]. 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[38-41]. 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[38,41,42]. 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[41,43]. 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

Table 3 Literature on argon plasma coagulation therapy use in chronic radiation proctopathy

Study Ref.	n	Mean age (yr) (range)	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	Follow-up duration mean (mo)	Complications/Side effects	% requiring trans-fusion
Swan et al[49], 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, fever in 1, and bleeding in 1); long-term: 1 (2%) asymptomatic rectal stricture	
Karamanolis et al[46], 2009	56	68.4 (45–86)	2.0 L/min, 40W	2 (1-8)	Mild (100%), severe (79%), total (89%)	N/A	7/9	17.9 (6-33)	one case of colonic explosion without perforation; No strictures or persistent ulcers; 2 on anticoagulation with recurrence	9/56 (16%)
Tormo et al[74], 2009	22	74.3	2 L/min, 50 W	2.58 (1-7), median-2	100%	N/A	N/A	N/A	None	2/22 (9%)
Alfadhli et al[14], 2008	14	74.7	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[75], 2008	38	70.9		3.6 ± 2.7		mean2.7 gm% mean increase		28		
Dees et al[76],2006	48		2 L/min, 50 W	Median-3	98%				Two patients-recurrent blood loss on anticoagulation; 1-ulcer	6/48 (12.5%)
Ben-Soussan et al[53], 2004	27	73.1 (53-86)	0.8-1.0 L/min, 40-50 W	2.66 (1-7)	92%			13.6 (3-31)	Side effects-anal/rectal pain (n = 3), vagal symptoms (n = 2), 3 colonic explosions-1 with perforation requiring surgery, no stricture	8/27 (30%)
Higuera et al[77], 2004	10		1.5-2.0 L/min, 60 W	1.9 (1-4), median (2)	100%	1.5-1.9 gm% mean increase	1/1 (100%)	31.1 (10-45)	No ulcers/strictures, 1 (10%)-tenesmus	
Sebastian et al[39], 2004	25	69 (53–77)	1.5 L/min, 30 W (25-40 W)	median-1	21/25 (76%, 81% or 84%??)	2.4 gm% mean increase		Median 14-	1-rectal pain	
Urban et al[78], 2004	8			1-4	100%					
Ravizza et al[51], 2003	27	72 (62-83)	3 L/min + 60 W (n = 17) reduced to 2 L/min and 40 W (n = 10)	2 (1-5)	85% marked improvement, 10/27 only had minor bleeding, 48% Complete resolution	3.2 g/dL mean increase	6/6 (100%) transfusion relief	11.5 (1-24)	Short term-2/27 (7%), 1-transient anal/rectal pain, 1-fever; long-14/27 (52%)-asymptomatic rectal ulcers	6/27
Gheorghe et al[58], 2003	42		60 W (23), 50 W (19)	1.34, 1.9						
Canard et al[48], 2003	30	70.7 (58-85)	0.8-2 L/min, 30-80 W	2.3 (1-5)	(87%)			20 (3-35)	Overall-47%; 3 severe (10%): 1 severe bleeding, 1 extensive necrosis of lower part of rectum, 1 perforation. 3 microrectitis and 2 asymptomatic rectal stenosis. Post-Rx pain in 6 patients (20%)	17%
Venkatesh et al[79], 2002	40	64-83	1-1.5 L/min, 40-60 W	Mean-1.35 median-1 (1-2)	97.5%	- 97.5% patients	20/21 (95.2%)	NR 3-30	1-urinary retention, 2-fever requiring antibiotics	21/40 (52.5%)
Taieb et al[80], 2001	11	73 (54-86)	0.8-2 L/min, 50W	3.2 (1-5)	82% CR, 18% PR	3.8 gm% mean increase	7/7 (100%)	19 (7-30)		7/11 (63.6%)
Tjandra et al[41], 2001	12		1.5L/min, 40 W	2 (1-3)	50% CR, 50% PR, 83% Signi	1.1 gm% mean increase	4/4 (100%)	11 (4-17)	None	4/12 (33%)
Smith et al[81], 2001	7		1.6 L/min, 40-45 W	1-3	71% CR, 29% PR			4-13	None	
Rolachon et al[82], 2000	12	70.3	1.0 L/min, 50 W	Mean (2.8 ± 0.8)	66% CR, 83% PR	1.8 gm% mean increase		6	3/12 (25%), 2-chronic rectal ulcerations, 1-asymptomatic rectal stenosis	
Kaassis et al[44], 2000	16	73.5 (62-80)	0.6 L/min, 40 W	Mean-3.7 (2-8)	44% CR, 56% PR		3/3 (100%)	10.7 (8-28)	No	3/16 (18.75%)
Tam et al[40], 2000	15		2 L/min, 60 W	Median-2 (1-4)	100%	2.5 gm% mean increase	3/3 (100%)	Median-24 (8-35)	2-asymptomatic rectal strictures requiring dilation	3/15 (20%)
Silva et al[45], 1999	28	65 (42-77)	1.5 L/min, 50 W	2.9 (1-8)	93%	1.2 gm% mean increase	-	10 (1-15)	No, 3-transient anal pain	15/28 (53%)
Fantin et al[62], 1999	7		3 L/min, 60 W	2 (2-4)	100%			Median 24 (18-24)	No	
Chutkan et al[83], 1997	12			1	92%			6.6	No	3/12 (25%)
Villavicencio et al[50], 2002	21	Median 72.6 (58-86)	1.2-2.0 L/min, 45-50 W	1.7 median (1-4)	95%	100% patients	4/4 (100%)	10.5 Median (1-29)	4-rectal pain, tenesmus, diarrhea	4/21 (19%)
Rotondano et al[84], 2003	24		0.8-1.2 L/min, 40 W	Median 2.5	100%				1-RV Fistula	
Zinicola et al[42], 2003	14		2 L/min, 65 W	2 (1-4)	86%%		3/3 (100%)	19 (5-41)	1-asymptomatic recto-sigmoid stenosis	3/14 (21%)

to respond to additional rounds of APC therapy[44,45].

Patients on anticoagulants or aspirin demonstrate higher recurrence[46]. Kaassis *et al*[44] 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*[47], 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*[48] 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. Alfadhli *et al*[14] and Swan *et al*[49] reported complications in 30%-35%. On the other hand, the experiences of Villavincencio *et al*[50] 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[50,51], and usually resolves spontaneously within few days or with standard analgesics[45,48,50,51]. 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[52]. Several authors have reported colonic explosion [1 of 56 (1.8%)[46] to 3 of 27 (11.1%)[53]] with or without perforation (Table 3) when the bowel has not been formally cleansed, and adequate colonic lavage is therefore a mandatory requirement[38,46,53,54]. 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[55].

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[50]. Ravizza *et al*[51] 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[51]. 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[56]. 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[51]. 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[51].

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%[49]-13.3%[40] (Table 3). A review of literature by Ravizza *et al*[51] 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 method. 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[48]. Duration of burn and power settings have also been correlated with depth of injury to the muscularis propria in swine colon[57]. 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[58]. Ravizza *et al*[51] 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, sucralfate 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*[51], 17 of their 27 patients had been treated unsuccessfully with corticosteroid or salicylate enemas. Tjandra *et al*[41,43] also found APC to be effective in 11 patients with CRP refractory to formalin therapy. Similarly in the study by Villavicencio *et al*[50], 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[50]. In a study by Zinicola *et al*[42], 6 (42.8%) patients had previously failed treatment with steroid enemas or 5-aminosalicylic acid enemas. In a recent study by Swan *et al*[49], 16 patients who failed in previous treatments for CRP all responded to endoscopic APC therapy. Alfadhli *et al*[14] 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 hematochezia. The rate of single-session APC responders (63.6%) was almost double that of the formalin-treated group (33.3%)[14].

RADIOFREQUENCY ABLATION

Radiofrequency ablation (RFA) with the BARRx Halo90 system has achieved superficial and broad fields of ablation in the esophagus[59,60] suggesting that similar benefits could be achieved in the colon and rectum. Zhou *et al*[61] 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 stricturing 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 rebleeding.

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 rebleeding and the relative lack of stricturing 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[18,22], or APC[44,62]. As with APC, the unit is mobile and can be used in different rooms of an endoscopic suite. The BARRx 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*[63] 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 ease of targeted application. Cryoablation works through immediate and delayed effects. Delayed effects are related to induction of ischemic necrosis.

Kantsevoy *et al*[64] 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[65]. Complete cessation of bleeding was achieved in all 7 (100%) patients who underwent cryoablation therapy for radiation proctitis. A major advantage of the cryotherapy 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*[66] 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*[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*[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)[68]. 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 ($P = 0.009$)[68]. Severe complication included one (10%) patient with cecal perforation secondary to over-insufflation 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[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 findings, 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 to minimize 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[9,10], then the neodymium/yttrium aluminum garnet[11,12] and potassium titanyl phosphate lasers[13,14], which were each effective. Formalin administration through a rigid scope also proved effective[15,16]. 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*[16] suggested possible scoring systems and outcome measures (including quality-of-life scores) that seem sensible in this disease. Adoption 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.

REFERENCES

1   **Haboubi NY**, Schofield PF, Rowland PL. The light and electron microscopic features of early and late phase radiation-

induced proctitis. *Am J Gastroenterol* 1988; **83**: 1140-1144

2   **Hasleton PS**, Carr N, Schofield PF. Vascular changes in radiation bowel disease. *Histopathology* 1985; **9**: 517-534

3   **Gilinsky NH,** Burns DG, Barbezat GO, Levin W, Myers HS, Marks IN. The natural history of radiation-induced proctosigmoiditis: an analysis of 88 patients. *Q J Med* 1983; **52**: 40-53

4   **Muthlu E,** Brunig K, Morrisey M. Quality of life of patients with radiation proctitis. *Gastroenterology* 2002; **12**: A193-194

5   **Counter SF,** Froese DP, Hart MJ. Prospective evaluation of formalin therapy for radiation proctitis. *Am J Surg* 1999; **177**: 396-398

6   **Kochhar R**, Patel F, Dhar A, Sharma SC, Ayyagari S, Aggarwal R, Goenka MK, Gupta BD, Mehta SK. Radiation-induced proctosigmoiditis. Prospective, randomized, double-blind controlled trial of oral sulfasalazine plus rectal steroids versus rectal sucralfate. *Dig Dis Sci* 1991; **36**: 103-107

7   **Baum CA**, Biddle WL, Miner PB. Failure of 5-aminosalicylic acid enemas to improve chronic radiation proctitis. *Dig Dis Sci* 1989; **34**: 758-760

8   **Talley NA,** Chen F, King D, Jones M, Talley NJ. Short-chain fatty acids in the treatment of radiation proctitis: a randomized, double-blind, placebo-controlled, cross-over pilot trial. *Dis Colon Rectum* 1997; **40**: 1046-1050

9   **Kennedy M**, Bruninga K, Mutlu EA, Losurdo J, Choudhary S, Keshavarzian A. Successful and sustained treatment of chronic radiation proctitis with antioxidant vitamins E and C. *Am J Gastroenterol* 2001; **96**: 1080-1084

10   **Hille A**, Christiansen H, Pradier O, Hermann RM, Siekmeyer B, Weiss E, Hilgers R, Hess CF, Schmidberger H. Effect of pentoxifylline and tocopherol on radiation proctitis/enteritis. *Strahlenther Onkol* 2005; **181**: 606-614

11   **Lucarotti ME**, Mountford RA, Bartolo DC. Surgical management of intestinal radiation injury. *Dis Colon Rectum* 1991; **34**: 865-869

12   **Cavcić J**, Turcić J, Martinac P, Jelinčić Z, Zupancić B, Panijan-Pezerović R, Unusić J. Metronidazole in the treatment of chronic radiation proctitis: clinical trial. *Croat Med J* 2000; **41**: 314-318

13   **Raman RR.** Two percent formalin retention enemas for hemorrhagic radiation proctitis: a preliminary report. *Dis Colon Rectum* 2007; **50:** 1032-1039

14   **Alfadhli AA**, Alazmi WM, Ponich T, Howard JM, Prokopiw I, Alaqeel A, Gregor JC. Efficacy of argon plasma coagulation compared to topical formalin application for chronic radiation proctopathy. *Can J Gastroenterol* 2008; **22:** 129-132

15   **Denton AS**, Andreyev HJ, Forbes A, Maher EJ. Systematic review for non-surgical interventions for the management of late radiation proctitis. *Br J Cancer* 2002; **87**: 134-143

16   **Denton A**, Forbes A, Andreyev J, Maher EJ. Non surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis. *Cochrane Database Syst Rev* 2002; (1): CD003455

17   **Clarke RE**, Tenorio LM, Hussey JR, Toklu AS, Cone DL, Hinojosa JG, Desai SP, Dominguez Parra L, Rodrigues SD, Long RJ, Walker MB. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. *Int J Radiat Oncol Biol Phys* 2008; **72**: 134-143

18   **Jensen DM,** Machicado GA, Cheng S, Jensen ME, Jutabha R. A randomized prospective study of endoscopic bipolar electrocoagulation and heater probe treatment of chronic rectal bleeding from radiation telangiectasia. *Gastrointest Endosc* 1997; **45**: 20-25

19   **Viggiano TR,** Zighelboim J, Ahlquist DA, Gostout CJ, Wang =bleeding from radiation proctopathy. *Gastrointest Endosc* 1993; **39**: 513-517

20   **Barbatzas C,** Spencer GM, Thorpe SM, Sargeant LR, Bown SG. Nd: YAG laser treatment for bleeding from radiation proctitis. *Endoscopy* 1996; **28**: 497-500

21   **Taylor JG,** Disario JA, Bjorkman DJ. KTP laser therapy for bleeding from chronic radiation proctopathy. *Gastrointest Endosc* 2000; **52**: 353-357

22   **Maunoury V,** Brunetaud JM, Cortot A. Bipolar electrocoagulation treatment for hemorrhagic radiation injury of the lower digestive tract. *Gastrointest Endosc* 1991; **37**: 492-493

23   **Johnstone J.** Complications following endoscopic laser therapy. *Gastrointest Endosc* 1982; **28:** 135-136

24   **Johnston MJ**, Robertson GM, Frizelle FA. Management of late complications of pelvic radiation in the rectum and anus: a review. *Dis Colon Rectum* 2003; **46:** 247-259

25   **Fuentes D**, Monserat R, Isern AM, Salazar J, Bronstein M, Gumina C, Fernandez C, Gori H, Sanchez MJ, Zaidman I. Colitis due to radiation: endoscopic management with heat probe. *GEN 1993*; **47**: 165-167

26   **Leuchter RS**, Petrilli ES, Dwyer RM, Hacker NF, Castaldo TW, Lagasse LD. Nd: YAG laser therapy of rectosigmoid bleeding due to radiation injury. *Obstet Gynecol* 1982; **59**: 65S-67S

27   **Swaroop VS**, Gostout CJ. Endoscopic treatment of chronic radiation proctopathy. *J Clin Gastroenterol* 1998; **27**: 36-40

28   **Wilson LC,** Giling PJ**.** Lasers for prostate surgery: an update. Business Briefing. *Eur Kidney Urol Dis* 2006; 1-5

29   **Ventrucci M,** Di Simone MP, Giulietti P, De Luca G. Efficacy and safety of Nd: YAG laser for the treatment of bleeding from radiation proctocolitis. *Dig Liver Dis* 2001; **33:** 230-233

30   **Pritikin J**, Weinman D, Harmatz A, Young H. Endoscopic laser therapy in gastroenterology. *West J Med* 1992; **157**: 48-54

31   **O'Connor JJ.** Argon laser treatment of radiation proctitis. *Arch Surg* 1989; **124**: 749

32   **Buchi KN,** Dixon JA. Argon laser treatment of hemorrhagic radiation proctitis. *Gastrointest Endosc* 1987 ; **33**: 27-30

33   **Taylor JG,** DiSario JA, Buchi KN. Argon laser therapy for hemorrhagic radiation proctitis: long-term results. *Gastrointest Endosc* 1993; **39**: 641-644

34   **Farin G,** Grund KE. Technology of argon plasma coagulation with particular regard to endoscopic applications. *Endosc Surg Allied Technol* 1994; **2**: 71-77

35   **Waye JD,** Grund KE, Farin G. Argon plasma coagulation (APC). Clinical usefulness in flexible endoscopy. *Gastrointest Endosc* 1996; **46:** A306

36   **Grund KE,** Straub T, Farin G. Clinical application of argon plasma coagulation in flexible endoscopy. *Endosc Digest* 1998; **10:** 1543–1554

37   **Grund KE,** Storek D, Farin G. Endoscopic argon plasma coagulation (APC) first clinical experiences in flexible endoscopy. *Endosc Surg Allied Technol* 1994; **2**: 42-46

38   **Postgate A**, Saunders B, Tjandra J, Vargo J. Argon plasma coagulation in chronic radiation proctitis. *Endoscopy* 2007; **39**: 361-365

39   **Sebastian S**, O'Connor H, O'Morain C, Buckley M. Argon plasma coagulation as first-line treatment for chronic radiation proctopathy. *J Gastroenterol Hepatol* 2004; **19**: 1169-1173

40   **Tam W**, Moore J, Schoeman M. Treatment of radiation proctitis with argon plasma coagulation. *Endoscopy* 2000; **32**: 667-672

41   **Tjandra JJ**, Sengupta S. Argon plasma coagulation is an effective treatment for refractory hemorrhagic radiation proctitis. *Dis Colon Rectum* 2001; **44**: 1759-1765; discussion 1771

42   **Zinicola R**, Rutter MD, Falasco G, Brooker JC, Cennamo V, Contini S, Saunders BP. Haemorrhagic radiation proctitis: endoscopic severity may be useful to guide therapy. *Int J Colorectal Dis* 2003; **18**: 439-444

43   **Tagkalidis PP**, Tjandra JJ. Chronic radiation proctitis. *ANZ J Surg* 2001; **71**: 230-237

44   **Kaassis M**, Oberti E, Burtin P, Boyer J. Argon plasma coagulation for the treatment of hemorrhagic radiation proctitis. *Endoscopy* 2000; **32**: 673-676

45   **Silva RA,** Correia AJ, Dias LM, Viana HL, Viana RL. Argon plasma coagulation therapy for hemorrhagic radiation proctosigmoiditis. *Gastrointest Endosc* 1999; **50:** 221-224

46   **Karamanolis G**, Triantafyllou K, Tsiamoulos Z, Polymeros D, Kalli T, Misailidis N, Ladas SD. Argon plasma coagulation has a long-lasting therapeutic effect in patients with chronic radiation proctitis. *Endoscopy* 2009; **41**: 529-531

47   **Coriat R**, Wolfers C, Chaput U, Chaussade S. Treatment of radiation-induced distal rectal lesions with argon plasma coagulation: use of a transparent cap. *Endoscopy* 2008; **40** Suppl 2: E270

48   **Canard JM**, Védrenne B, Bors G, Claude P, Bader R, Sondag D. [Long term results of treatment of hemorrhagic radiation proctitis by argon plasma coagulation]. *Gastroenterol Clin Biol* 2003; **27**: 455-459

49   **Swan MP,** Moore GT, Sievert W, Devonshire DA. Efficacy and safety of single-session argon plasma coagulation in the management of chronic radiation proctitis. *Gastrointest Endosc* 2010; **72**: 150-154

50   **Villavicencio RT**, Rex DK, Rahmani E. Efficacy and complications of argon plasma coagulation for hematochezia related to radiation proctopathy. *Gastrointest Endosc* 2002; **55**: 70-74

51   **Ravizza D**, Fiori G, Trovato C, Crosta C. Frequency and outcomes of rectal ulcers during argon plasma coagulation for chronic radiation-induced proctopathy. *Gastrointest Endosc* 2003; **57**: 519-525

52   **Morrow JB,** Dumot JA, Vargo JJ. Radiation-induced hemorrhagic carditis treated with argon plasma coagulator. *Gastrointest Endosc* 2000; **51**: 498-499

53   **Ben-Soussan E,** Antonietti M, Savoye G, Herve S, Ducrotté P, Lerebours E. Argon plasma coagulation in the treatment of hemorrhagic radiation proctitis is efficient but requires a perfect colonic cleansing to be safe. *Eur J Gastroenterol Hepatol* 2004; **16**: 1315-1318

54   **Ladas SD**, Karamanolis G, Ben-Soussan E. Colonic gas explosion during therapeutic colonoscopy with electrocautery. *World J Gastroenterol* 2007; **13**: 5295-5298

55   **Reddy C**, Majid A, Michaud G, Feller-Kopman D, Eberhardt R, Herth F, Ernst A. Gas embolism following bronchoscopic argon plasma coagulation: a case series. *Chest* 2008; **134**: 1066-1069

56   **Eisen GM**, Dominitz JA, Faigel DO, Goldstein JL, Kalloo AN, Petersen JL, Raddawi HM, Ryan ME, Vargo JJ, Young HS, Fanelli RD, Hyman NH, Wheeler-Harbaugh J. Endoscopic therapy of anorectal disorders. *Gastrointest Endosc* 2001; **53**: 867-870

57   **Norton ID**, Wang L, Levine SA, Burgart LJ, Hofmeister EK, Yacavone RF, Gostout CJ, Petersen BT. In vivo characterization of colonic thermal injury caused by argon plasma coagulation. *Gastrointest Endosc* 2002; **55**: 631-636

58   **Gheorghe C**, Gheorghe L, Iacob R, Iacob S, Simionov I, Băncilă I. Argon plasma coagulation for radiation proctitis. *Rom J Gastroenterol* 2003; **12**: 107-112

59   **Sharma VK**, Wang KK, Overholt BF, Lightdale CJ, Fennerty MB, Dean PJ, Pleskow DK, Chuttani R, Reymunde A, Santiago N, Chang KJ, Kimmey MB, Fleischer DE. Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett's esophagus: 1-year follow-up of 100 patients. *Gastrointest Endosc* 2007; **65**: 185-195

60   **Mashimo H**, Chen Y, Huang SW, Huang Q, Aguirre A, Schmitt J, Fujimoto J. Endoscopic optical coherence tomography reveals Barrett's Underneath squamous neo-epithelium after radiofrequency ablation. *Gastroenterology* 2007; **132**: A96-A96

61   **Zhou C**, Adler DC, Becker L, Chen Y, Tsai TH, Figueiredo M, Schmitt JM, Fujimoto JG, Mashimo H. Effective treatment of chronic radiation proctitis using radiofrequency ablation. *Therap Adv Gastroenterol* 2009; **2**: 149-156

62   **Fantin AC,** Binek J, Suter WR, Meyenberger C. Argon beam coagulation for treatment of symptomatic radiation-induced proctitis. *Gastrointest Endosc* 1999; **49**: 515-518

63   **Nikfarjam M,** Faulx A, Laughinghouse M, Marks JM. Feasibility of radiofrequency ablation for the treatment of chronic radiation proctitis. *Surg Innov* 2010; **17**: 92-94

64   **Kantsevoy SV**, Cruz-Correa MR, Vaughn CA, Jagannath SB, Pasricha PJ, Kalloo AN. Endoscopic cryotherapy for the treatment of bleeding mucosal vascular lesions of the GI tract: a pilot study. *Gastrointest Endosc* 2003; **57**: 403-406

65   **Pasricha PJ,** Hill S, Wadwa KS, Gislason GT, Okolo PI, Magee CA, Canto MI, Kuo WH, Baust JG, Kalloo AN. Endoscopic cryotherapy: experimental results and first clinical use. *Gastrointest Endosc* 1999; **49**: 627-631

66   **Shaib Y,** Hou J. Complete endoscopic healing of radiation proctitis with low pressure cryoablation. *Am J Gastroenterol* 2008; **103** Suppl 1**:** S230

67   **Battish R,** Shah H, Bashir R. Short-term Follow-up of Cryoablation Treatment for Radiation Proctitis. *Am J Gastroenterol* 2009; **104:** S390

68   **Hou JK**, Abudayyeh S, Shaib Y. Treatment of chronic radiation proctitis with cryoablation. *Gastrointest Endosc* 2011; **73:** 383-389

69   **Haulk A.** Bipolar cautery effectively controls bleeding due to radiation proctitis. *Gastroenterology* 1996; **110:** A328

70   **Chapuis P,** Dent O, Bokey E, Galt E, Zelas P, Nicholls M, Yuile P, Mameghan H. The development of a treatment protocol for patients with chronic radiation-induced rectal bleeding. *Aust N Z J Surg* 1996; **66:** 680-685

71   **Jacobs M.** YAG laser treatment for radiation proctitis. *Gastrointest Endosc* 1989; **35:** 355-356

72   **Alexander TJ,** Dwyer RM. Endoscopic Nd: YAG laser treatment of severe radiation injury of the lower gastrointestinal tract: long-term follow-up. *Gastrointest Endosc* 1998; **34:** 407-411

73   **Ahlquist DA**, Gostout CJ, Viggiano TR, Pemberton JH. Laser therapy for severe radiation-induced rectal bleeding. *Mayo Clin Proc* 1986; **61:** 927-931

74   **Tormo V,** Wikman Jorgensen P, García del Castillo G, Ruiz F, Martínez Egea A. Effectiveness of argon plasma coagulation in the treatment of chronic actinic proc. *Rev Esp Enferm Dig* 2009; **101:** 91-93, 94-96

75   **Latorre Sánchez M,** Sempere García-Argüelles J, Barceló Cerdá S, Huguet Malaves JM, Canelles Gamir P, Quiles Teodoro F, Medina Chuliá E. [Evaluation of the endoscopic response to argon plasma coagulation in patients with chronic radiation proctopathy]. *Rev Esp Enferm Dig* 2008; **100:** 619-624

76   **Dees J**, Meijssen MA, Kuipers EJ. Argon plasma coagulation for radiation proctitis. *Scand J Gastroenterol Suppl* 2006; (243): 175-178

77   **de la Serna Higuera C**, Martín Arribas M, Rodríguez Gómez S, Pérez Villoria A, Martínez Moreno J, Betancourt González A. Efficacy and safety of argon plasma coagulation for the treatment of hemorrhagic radiation proctitis. *Rev Esp Enferm Dig* 2004; **96:** 758-764

78   **Urban O**, Chalupa J, Vítek P, Reha P. [Treatment of chronic postirradiation proctitis with argon plasma coagulation]. *Vnitr Lek* 2004; **50:** 218-221

79   **Venkatesh KS**, Ramanujam P. Endoscopic therapy for radiation proctitis-induced hemorrhage in patients with prostatic carcinoma using argon plasma coagulator application. *Surg Endosc* 2002; **16:** 707-710

80   **Taïeb S,** Rolachon A, Cenni JC, Nancey S, Bonvoisin S, Descos L, Fournet J, Gérard JP, Flourié B. Effective use of argon plasma coagulation in the treatment of severe radiation proctitis. *Dis Colon Rectum* 2001; **44:** 1766-1771

81   **Smith S,** Wallner K, Dominitz JA, Han B, True L, Sutlief S, Billingsley K. Argon plasma coagulation for rectal bleeding after prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2001; **51:** 636-642

82   **Rolachon A,** Papillon E, Fournet J. [Is argon plasma coagulation an efficient treatment for digestive system vascular malformation and radiation proctitis?]. *Gastroenterol Clin Biol* 2000; **24:** 1205-1210

83   **Chutkan R,** Lipp A, Waye J. The argon plasma coagulator: A new and effective modality for treatment of radiation proctitis. *Gastrointest Endosc* 1997; **45:** AB27

84   **Rotondano G,** Bianco MA, Marmo R, Piscopo R, Cipolletta L. Long-term outcome of argon plasma coagulation therapy for bleeding caused by chronic radiation proctopathy. *Dig Liver Dis* 2003; **35:** 806-810