Medical Management of Radiation Effects on the Intestines

15

Deepak Parakkal and Eli D. Ehrenpreis

Introduction

Despite advances in the delivery of pelvic radiotherapy, radiation exposure to the small and large intestines, as "innocent bystanders," remains a significant dose-limiting factor. The gastrointestinal (GI) tract is the most prominent organ developing chronic toxicity associated with radiation treatment. Conservative estimates of the number of patients with postradiation intestinal dysfunction living in the United States of America exceed 1 million and likely approaches 2 million persons [1]. In this chapter, we discuss evolving therapeutic options for treatment of acute and chronic radiation injury to the GI tract divided anatomically between the intestines (small and large) and the rectum (and anus) followed by a discussion of preventive strategies.

Eli D. Ehrenpreis (✉)
NorthShore University HealthSystem
Gastroenterology Division
Center for the Study of Complex Diseases

University of Chicago Pritzker School of Medicine
e-mail: ehrenpreis@gipharm.net

D. Parakkal
Gastroenterology and Hepatology, Mayo Clinic,
Rochester, MN, USA
e-mail: deepak.parakkal@gmail.com

Intestinal Involvement: Enteropathy and Colopathy

Acute Radiation Enteropathy

The most common symptoms of acute radiation enteropathy include diarrhea, abdominal cramping or pain, nausea and vomiting, anorexia, and malaise. Most cases are self-limited, requiring only supportive treatment with antidiarrheal medications (loperamide, diphenoxylate with atropine, other anticholinergic agents, and opioids), sometimes in combination with antiemetic agents (Table 15.1). Dietary modifications such as low-fat, lactose-free diets have been recommended to improve symptoms. A double-blind placebo-controlled trial evaluated oral sucralfate (1 g six times a day) in 70 patients with carcinoma of the prostate or urinary bladder receiving pelvic irradiation. Each patient received sucralfate 2 weeks after radiation was started. Treatment was continued for a total of 6 weeks. The study showed a decrease in frequency and improvement in consistency of bowel movements, as well as improved chronic symptoms 1 year after completion of radiation treatment [2]. Animal models have shown some benefit of pretreatment with bile salts binders such as cholestyramine. Rats received 4 g of cholestyramine per day for 10 days followed by 1000 rads of mid-abdominal radiation. A significant decrease in diarrhea was seen in the treated group (45%) compared to the control group (67%, $p<0.05$) [3]. A double-blind, randomized

Eli D. Ehrenpreis et al. (eds.), *Radiation Therapy for Pelvic Malignancy and its Consequences,*
DOI 10.1007/978-1-4939-2217-8_15, © Springer Science+Business Media New York 2015

Table 15.1 Medical management of radiation enteropathy

Acute radiation enteropathy
Antidiarrheal medications
Low-fat, lactose-free diets
Oral sucralfate
Oral cholestyramine
Acetylsalicylate
Parental fluids
Chronic radiation enteropathy
Low-residue lactose-free diet
Total parenteral nutrition
Antidiarrheal medications
Antibiotics
5–Aminosalicylates
Hyperbaric oxygen therapy

trial was performed to evaluate anti-inflammatory agents (acetylsalicylate) in 28 women receiving pelvic radiation for uterine cancer. A significant reduction in the number of bowel movements was seen in the treated group (78.6% decreased vs 21.4% decreased, $p<0.004$). There was complete reduction in colicky abdominal pain ($p<0.001$), and flatulence ($p<0.03$) was seen in the treatment group compared while no reduction of these symptoms occurred in the controls [4].

Administration of parenteral fluids and electrolytes may be helpful to prevent and treat dehydration.

Chronic Radiation Enteropathy

Minimizing small intestinal exposure to radiation is paramount in avoiding chronic radiation enteropathy. However, once established, recommend treatment for patients with chronic radiation enteropathy that is not complicated by intestinal obstruction, perforation, or fistula formation is usually conservative and focused on relief of symptoms. Some therapeutic options are discussed below and are shown in Table 15.1.

Nutritional management—Vitamin and micronutrient deficiencies need to be corrected. A low-residue diet is often advised as even normal portions of foods with moderate-high fiber content may worsen diarrhea and urgency [5]. Lactose intolerance, secondary to small intestinal injury as well as bacterial overgrowth, may improve following antibiotic treatment (described below) and avoidance of lactose [1].

Total parenteral nutrition (TPN) is a mainstay of the medical therapy for patients with severe chronic radiation enteropathy and patients requiring intestinal resection. The application of TPN has approximately the same degree of success seen in other intestinal disorders [6]. In the largest study of this modality to date, 54 patients (39 women and 15 men) with radiation enteropathy who received home TPN were evaluated. TPN was initiated at a median of 20 months (range 2–432) after beginning radiation therapy [7]. The causes of intestinal failure resulting from radiation therapy in these patients were intestinal obstruction (27 patients), short bowel syndrome [17], malabsorption [5], enteric fistulas [3], and dysmotility [2]. The mean duration of TPN was 20.4 months (range 2–108 months) with an overall estimated probability of 5-year survival of 64%. Another study compared the long-term outcome of 30 patients with radiation-induced intestinal obstruction treated either surgically (17 patients) or with intestinal rest and home parenteral nutrition (13 patients) [8]. Nutritional autonomy and 5-year survival were 100% and 90%, respectively, in the home TPN group versus 59% and 68%, respectively, in the surgically treated group.

Intestinal Dysmotility

Use of antidiarrheal agents (such as loperamide) can help improve diarrhea if stricturing and obstruction of the bowel have been ruled out. The efficacy of loperamide was evaluated in a trial involving 18 patients with diarrhea secondary to chronic radiation enteropathy. The participants were randomly assigned to loperamide or placebo for 14 days separated by a 14-day washout period, followed by a crossover [9]. Loperamide was associated with a significant reduction in the frequency of bowel movements, slower intestinal transit as measured using radiopaque markers, and improved absorption of bile acids [9].

Small Intestinal Bacterial Overgrowth (SIBO)

Patients with chronic radiation enteropathy are at risk for SIBO. Some have suggested testing for bacterial overgrowth and using antibiotics to reduce symptoms in those patients that test positive [1]

Other Therapeutic Options

5-Acetylsalicylic acid (ASA) drugs—A case study of four patients with chronic radiation enteropathy suggested a possible benefit from sulfasalazine with or without oral prednisone. Positive effects were evidenced by both radiographic as well as clinical improvement in stool frequency [10].

Hyperbaric oxygen—Hyperbaric oxygen (HBO) therapy has been used to treat chronic radiation enteropathy. Its beneficial effects have been attributed to inhibition of small intestinal bacterial growth [11], and decreased bacterial toxin production [12]. Other possible mechanisms include the production of an oxygen gradient within a hypoxic tissue bed that stimulates neovascularization, improving the blood supply, and reversing ischemia and necrosis responsible for severe complications [13]. The beneficial effect of HBO in chronic radiation enteropathy was first published as a case report of a patient who received 20 treatments over 1-month period with objective improvements in symptoms and absorption of D-xylose [14]. HBO was also noted to be useful in treating a patient with severe hypomagnesemia secondary to radiation enteropathy [15]. A retrospective study of 36 patients with severe radiation enteropathy refractory to medical management was performed. Patients received an average of 67 sessions of HBO at 2.5 atmospheres. Improvement of clinical signs and symptoms (wound healing, rectal bleeding, profuse diarrhea, and/or recurrent anal abscess) was reported in two-thirds of the patients [16].

HBO may also be helpful in management of bleeding due to chronic radiation enteropathy not controlled with other measures such as laser therapy and formalin [17]. In a large clinical series of 65 consecutive patients with chronic radiation enteropathy (primarily manifested as chronic bleeding), an initial treatment with 30 consecutive daily treatments of HBO was given at 2.36 atmospheres. The response rate (defined as a greater than 50% reduction of bleeding), was 70%. Response for other symptoms (pain, diarrhea, weight loss, fistula, and obstruction) was 58% [18]. There are a number of studies demonstrating the beneficial effects of HBO for radiation proctopathy as described later in this chapter.

Several issues are associated with the use of HBO in this setting. Equipment needed for HBO is expensive and requires the local availability of specialized centers. Side effects of HBO therapies are usually mild and reversible but can be severe and life threatening [19]. In general, if pressures do not exceed 300 kPa and the length of treatment is less than 120 min, HBO therapy is considered to be safe. Reversible myopia, due to oxygen toxicity to the lens, the commonest side effect, occurs in up to 20% of patients [19]. Symptomatic otic barotrauma (that is reversible) occurs in 15–20% of patients and pulmonary symptoms are present in 15–20%. Severe central nervous system symptoms such as seizures are seen in 1–2% of treated patients. These do not typically result in permanent structural brain damage [19].

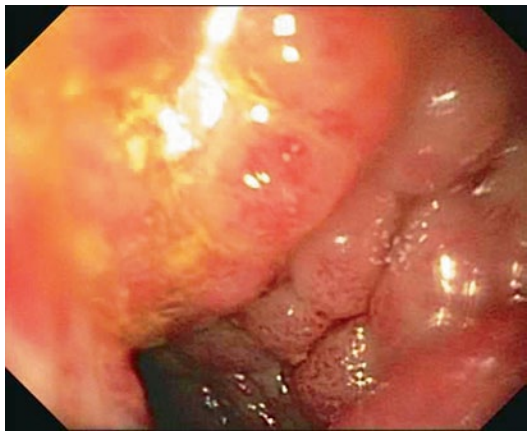

Fig. 15.1 Endoscopic appearance of a patient with chronic radiation colopathy and lower gastrointestinal bleeding

Large Intestine

Specific treatments for large intestinal injury or colopathy (not including the rectum) have not been determined in clinical trials. Symptomatic management for acute colopathy with antidiarrheal agents is recommended. Management of chronic colopathy at this point is similar from a clinical standpoint to the management of chronic radiation proctopathy and is covered in the next section. These treatments are often directed at reducing bleeding from colonic telangiectasias (see Fig. 15.1)

Rectum

Acute Radiation Proctopathy

Treatment of acute radiation proctopathy generally is directed at symptomatic relief. Topical lignocaine preparations may have a soothing effect for anorectal irritation, and loperamide will reduce stool, frequency, and tenesmus [1]. When inflammatory symptoms such as anorectal urgency and tenesmus are severe, use of corticosteroid-containing suppositories has been suggested [1]. Butyrate enemas may work to accelerate healing in acute radiation proctopathy. In a randomized, double-blind, crossover protocol, 20 patients (11 male and 9 female) presenting with acute radiation proctopathy within 3 weeks of radiation therapy for malignant pelvic disease were treated for 3 weeks each with topical sodium butyrate or saline enemas [20]. Patients were assessed clinically, endoscopically, and histologically before entry to the study, at week 3, and at the end of the study. Topical butyrate, led to remission of symptoms. This effect was not seen in the saline group. Clinical scores decreased from 8.2 (SE 1.6) to 1.5 (0.7) in the butyrate-treated group but no change was seen in the saline-treated group (clinical score 7.9 (SE 1.8) to 8.1 (3.4)). Furthermore, crossover resulted in eight out of nine of the patients treated previously with placebo going into remission. Three patients previously treated with butyrate relapsed when switched to saline enemas.

Another study prospectively evaluated 31 patients with radiation-induced acute grade II proctopathy (increased stool frequency, bleeding, mucus discharge, rectal discomfort requiring medication, or anal fissure) per Common Toxicity Criteria (CTC) [21]. Twenty-three of 31 patients (74%) experienced a decrease of CTC grade within 8 days of treatment with sodium butyrate enemas. A statistically significant decrease in the incidence and severity (CTC grade) of proctopathy after 14 days of butyrate enema treatment and at the end of the treatment course with radiation (compared to before the start of treatment) was seen. There was no preventive effect on the incidence and severity of chronic radiation proctopathy.

Chronic Radiation Proctopathy

Two forms of symptoms of chronic radiation proctopathy occur, based on the pathophysiology of the disease. Rectal bleeding occurs from mucosal telangiectasias and ulcerations while chronic functional symptoms including urgency, tenesmus, and pain are due to loss of rectal compliance. At present, most of the literature on treatment of radiation proctopathy has focused on reduction of bleeding, leaving few therapeutic options for patients with functional symptoms. In addition, failure to recognize the importance

Table 15.2 Medical management of chronic radiation proctopathy

Nonendoscopic management
Sucralfate (rectal administration, oral has less evidence)
Oral metronidazole (in combination with oral 5-aminosalicylates and corticosteroid enema)
Oral vitamin E and C in combination (weak evidence)
Oral retinyl palmitate (vitamin A)
Hyperbaric oxygen therapy
Formalin (dab technique or instillation in rectum)
Short chain fatty acid enemas (weak evidence for long-term management)
Oral 5-aminosalicylate (in combination with corticosteroid enemas)
Endoscopic management
Argon laser
Nd:YAG laser
Bipolar electrocoagulation
Heater probe electrocoagulation
Argon plasma coagulation
Cryoablation

Nd:YAG neodymium-doped yttrium aluminum garnet

of these functional symptoms in patients has resulted in an underestimation of the prevalence of symptomatic chronic radiation proctopathy. Natural history studies suggest that in patients with low-grade rectal bleeding, 35% stopped bleeding spontaneously by 6 months [22]. In contrast, patients whose symptoms are more severe requiring frequent blood transfusions or are predominantly pain and bowel dysfunction, do not have such a favorable prognosis and require treatment.

A systematic review of nonsurgical interventions for chronic radiation proctopathy (updated in 2009) analyzing nine randomized controlled trials and one phase II study found insufficient data to make firm conclusions regarding any therapy for either bleeding or functional symptoms [23]. Some treatments (e.g., rectal sucralfate, metronidazole combined with topical anti-inflammatory treatment, and heater probe application) were reported to appear promising. Short chain fatty acid enemas were reported to be no more effective than placebo ($n=2$ studies). Heater probe compared to the use of bipolar electrocautery ($n=1$ study), showed no discernible differences in severe bleeding after 1 year, but was associated with a greater increase in the hematocrit and reduced transfusion requirements. Other modalities identified included the use of HBO and retinyl palmitate. All of these therapeutic options are discussed below in detail including nonendoscopic medical options and endoscopic approaches (see Table 15.2).

Nonendoscopic Medical Management

Sucralfate—Sucralfate may play a role in ulcer healing by promoting angiogenesis mediated via its interaction with basic fibroblast growth factor (bFGF) and increasing mucosal glutathione [24]. A prospective, double-blind trial evaluated 37 patients with chronic radiation-induced proctosigmoiditis, compared a 4-week course of either 3.0 g oral sulfasalazine plus 20 mg twice daily rectal prednisolone enemas versus 2.0 g twice daily rectal sucralfate enemas plus oral placebo [25]. The groups were evaluated clinically using a composite score for diarrhea, bleeding, and tenesmus classified into three grades: I (≤ 2 points), II (3–4 points), or III (≥ 5 points) and used endoscopic criteria of developed by Gilinsky et al.: mild/grade I (erythema ± telangiectasia, edema, thickening, pallor), moderate/grade II (above plus friability), or severe/grade III (ulceration ± necrosis). Although clinical and endoscopic improvement was noted in both groups, the clinical response was better for sucralfate enemas. These were also better tolerated. Another study conducted by the same authors evaluated

longer duration of therapy with sucralfate enemas in 26 patients with moderate-to-severe radiation proctosigmoiditis [26]. Patients were treated with sucralfate enemas (20 mL of a 10% suspension twice daily) until bleeding stopped or failure of therapy was acknowledged. Severity of rectal bleeding was graded as severe (≥15 bleeding episodes per week), moderate (8±14 episodes per week), mild (2±7 episodes per week), negligible (0±1 episode per week), or normal (no bleeding). Response to therapy was considered to be an improvement in the severity of bleeding by two grades. Rectally administered sucralfate achieved good response in 20 (76.9%) patients at 4 weeks, 22 (84.6%) patients at 8 weeks, and 24 (92.3%) patients at 16 weeks ($P<0.01$).

Successful treatment with oral sucralfate was initially reported in a case series involving three cases of hemorrhagic chronic postradiation proctopathy. All patients demonstrated decreased bleeding in the long-term follow-up period [27].

Metronidazole—The effectiveness of metronidazole in combination with corticosteroids enema and mesalazine was evaluated in a randomized study involving 60 patients with chronic radiation proctopathy (bleeding and diarrhea) [28]. Patients were divided into two equal groups and treated with mesalazine (3 g orally per day) and betamethasone enema (once a day) with or without metronidazole (1200 mg orally per day). The groups were compared for both clinical symptoms (diarrhea and rectal bleeding, with scores between 0 and 3) and rectosigmoidoscopic findings (rectal erythema, ulcers, and/or telangiectasias). The incidence of diarrhea and rectal bleeding was significantly lower in the metronidazole group at 4 weeks, 3 months, and 12 months, respectively. Similarly, endoscopic findings of erythema and mucosal ulcers were also lower in the metronidazole group at 4 weeks after treatment.

Vitamins—The antioxidant vitamins E and C have been postulated to prevent tissue damage in radiation injury and ischemia/reperfusion injury. Twenty consecutive symptomatic outpatients with endoscopically documented findings of chronic radiation proctopathy following pelvic radiotherapy were given a combination of vitamin E (400 IU tid) and vitamin C (500 mg tid) for a minimum of 4 weeks [29]. A significant ($p<0.05$) improvement was reported in a symptom index (before vs after treatment with vitamins E and C) for bleeding (median score: 4 vs 0), diarrhea (median score: 5 vs 0), and urgency (median score: 6 vs 3), but not rectal pain. Since the study had a poor follow-up, a control group was absent, and the fact that these vitamin doses may predispose to toxic side effects, these findings need confirmation with a controlled trial.

Vitamin A (retinyl palmitate) has been demonstrated to accelerate wound healing after burn injury and surgeries in laboratory animals, possibly secondary to increased cross-linking of collagen and myofibrils. In the only controlled trial performed to evaluate patients with functional symptoms of radiation proctopathy, our group investigated retinyl palmitate 10,000 IU by mouth for 90 days in randomized, double blind placebo-controlled trial in 19 patients (ten with retinyl palmitate and nine with placebo). Symptoms were scored using a novel scale termed the Radiation Proctopathy System Assessments Scale (RPSAS) [30]. Symptoms measured for severity and frequencies using the RPSAS were diarrhea, rectal urgency, rectal pain, difficulty initiating evacuation, rectal bleeding, and fecal incontinence. The severity of symptoms was scored from 1 to 5 while frequency was scored from 0 to 5. Seven of ten retinyl palmitate patients responded, whereas two of nine responded to placebo ($P=0.057$). The mean pre- and post-treatment change in RPSAS was 11±5 in the retinyl palmitate group and 2.5±3.6 in the placebo group ($P=0.013$). Additionally, all five placebo nonresponders who were crossed over to treatment with retinyl palmitate responded to treatment.

Hyperbaric oxygen—A potential role for HBO has been described in an observational study involving 27 patients with chronic radiation proctopathy secondary to pelvic radiotherapy for prostate cancer [31]. Patients received HBO at a pressure of 2.4 atmospheres absolute for 90 min 5–7 days weekly for an average of 36 sessions (range 29–60). Overall 67% of patients had

a partial to good response; while 33% showed no response or disease progression. A randomized, sham controlled, double-blind crossover trial evaluated 120 patients with chronic radiation proctopathy, randomized to receive to HBO at 2.0 atmospheres absolute (Group 1) or air at 1.1 atmospheres absolute (Group 2) [32]. The primary outcome measures were the late effects normal tissue subjective, objective, management, analytic (SOMA-LENT) score and standardized clinical assessment. For Group 1, the mean SOMA-LENT score was lower ($p=0.0150$) and the amount of improvement nearly twice as great (5.00 vs 2.61, $p=0.0019$) as Group 2. Similarly, Group 1 also had a greater portion of responders per clinical assessment than did Group 2 (88.9% vs 62.5%, respectively; $p=0.0009$). After completion of the crossover, no differences were detected ($p=0.6594$). The authors concluded that HBO therapy significantly improved the healing responses in patients with refractory radiation proctopathy, generating an absolute risk reduction of 32% (number needed to treat of 3) between the groups after the initial allocation. Adverse events associated with HBO therapy described in this study included ear pain in 19 patients (16%), transient myopia in four (3%), and confinement anxiety in two (1.7%) patients.

Formalin—Formalin is a mixture containing formaldehyde and methanol. The rationale for its use in chronic radiation proctopathy presenting with bleeding is that formalin-induced denaturation of proteins cause local chemical cauterization of telangiectatic mucosal vessels [33]. Application of formalin has been described in various studies either by "dabbing" it on to bleeding and telangiectatic spots on the rectal mucosa with a pledget of formalin-soaked gauze or cotton-tip applicator, or by "instilling" the solution in single or multiple aliquots into the rectum. The volume of formalin aliquots per installation and total volume (between 250 and 2000 mL) reported has been variable. While most studies of dab and instillation methods have used 4% formalin, one of the studies utilized a 10% formalin dab [34]. Aside from endoscopic flushing and removal of residual formaldehyde with saline, protection of the anoderm is advised. Intrarectal formalin therapy, particularly using the instillation technique is associated with significant morbidity including rectal strictures, intractable anal fissures, and the development of formalin colopathy (Fig. 15.2).

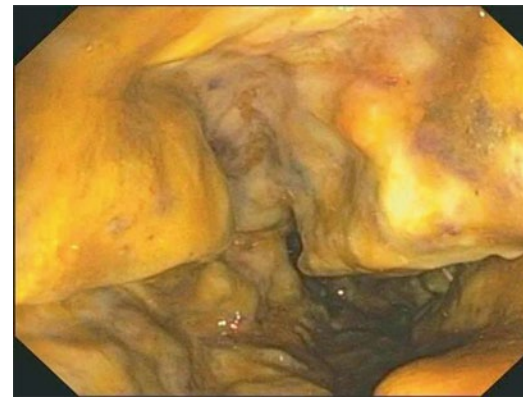

Fig. 15.2 Sigmoidoscopic view of severe formalin colopathy

In a prospective study, 33 patients with chronic radiation proctopathy received treatment with 4% formalin using the "dabbing" technique [33]. One application was performed in 23 patients while ten patients required a second application because of the persistent bleeding. The treatment was effective in 23 cases (70%): 13 patients with complete cessation of bleeding and ten patients with residual minor bleeding. The study reported morbidity secondary to the application with six anal or rectal strictures, four of whom had been treated for anal cancer. These were all successfully managed with dilation. Additionally, fecal incontinence worsened in 5 of the 11 patients who had received radiation therapy for anal cancer (45%) and occurred in 4 of the 22 other patients (18%). The authors emphasized concerns about local morbidity with this technique. Another study ($n=100$) investigated the direct application of a 10% buffered formalin solution using a 16-inch cotton tip applicator [34]. Overall, 93% of patients had cessation of bleeding after an average of 3.5 formalin applications at 2-week to 4-week intervals. Of note, this study only had a 4% complication rate (three patients with anal pain and one patient with postprocedure dizziness).

Formalin instillation technique involves administration of small aliquots of about 40–60 mL each, up to a total to 500 mL, with a dwell time in the rectum usually of 30 s. This method is usually performed in the operating room, using a perianal block and sedation, with perianal skin and sigmoid colon protection. The largest study of formalin instillation evaluated 20 female patients with hemorrhagic chronic radiation proctopathy who had failed treatment with topical steroids and/or mesalazine [35]. The study utilized 500 mL of 4% formalin instilled into the rectum in 50-mL aliquots. While the study had an overall success of 90%, five patients (25%) had moderate pelvic pain after instillation and one developed rectosigmoid colon necrosis that required resection plus a Hartmann procedure. Two patients developed rectovaginal fistulas that required a colostomy. One of these further required an abdominoperineal resection en bloc with the posterior wall of the vagina due to pelvis sepsis. Larger volumes and longer dwell times have also been associated with toxic levels of formic acid in the blood [36]. These adverse consequences of the formalin instillation technique suggest that this method should be abandoned except perhaps in cases of extensive rectosigmoid involvement not amenable to Argon Plasma Coagulation (APC) or formalin dab technique.

Short-chain fatty acid enemas—Short-chain fatty acid (SCFA) enemas may be effective in the short-term management of chronic hemorrhagic radiation proctopathy by inhibiting the inflammatory response including the NF-κB pathway. A prospective, randomized, double-blind, placebo-controlled trial evaluated treatment with SCFA enema (60 mM sodium acetate, 30 mM sodium propionate, and 40 mM sodium butyrate) in 19 patients with ongoing hemorrhage secondary to chronic radiation proctopathy [37]. Study endpoints included changes in the number of days in the week with rectal bleeding, hemoglobin measurements, endoscopic score (hyperemia and neovascularization), friability, edema and erosions. After a 5-week treatment period, the SCFA enema group showed a significant decrease in the number of days with rectal bleeding from the previous week (4.4+/−1.8 to 1.4+/−2.2; $P=0.001$) and an improvement of their endoscopic scores (4.8+/−1.4 to 2.2+/−1.2; $P=0.001$). However, after a 6- month follow-up, differences between the two groups were no longer observed.

Pentosan polysulfate—Pentosan polysulfate (PPS) a glycosaminoglycan, is a semisynthetic sulfated polyanion with heparin-like properties shown to be effective in treating radiation-induced sequelae of the bladder. A multicenter phase III study was performed. Fifty-seven patients received 100 mg PPS three times per day, 53 patients who received 200 mg PPS three times per day and 59 patients that received placebo [38]. Response to the treatment was measured as either complete or partial. Quality of life endpoints were measured using both a symptom assessment questionnaire, the Functional Alterations Due to Changes in Elimination, as well as general quality of questionnaires—the Medical Outcomes Survey and the Spitzer Quality of Life Index. The study failed to show any differences in response rates or quality of life measures compared to placebo.

Sulfasalazine and aminosalicylates—An initial pilot study of oral aminosalicylate in four patients with chronic radiation enteropathy and/or colopathy showed striking clinical progress accompanied by improvement in radiological appearance [10]. However, another pilot trial evaluating 5-aminosalicylic acid enemas in four patients with chronic radiation proctopathy failed to show any sustained benefit in symptoms (bleeding, pain, or tenesmus) or degree of mucosal inflammation on follow-up sigmoidoscopies [39]. A prospective, double-blind trial comparing sucralfate enema plus placebo to 3.0 g sulfasalazine and 20 mg twice daily rectal prednisolone enemas, showed significant clinical and endoscopic improvement in the 15 patients receiving sulfasalazine and prednisolone at 4 weeks [25].

Hormonal therapy—A single case report described the use of estrogen-progesterone combination therapy (ethinyl estradiol 0.07 mg/day, norethisterone 1 mg/day) in a patient with hemorrhagic chronic radiation proctopathy, with reduction in the requirement for blood transfusions and hospitalizations [40]. However, the therapy has been associated with serious side effects including thromboembolism.

Endoscopic Management of Bleeding

Because rectal bleeding in chronic radiation proctopathy is primarily due to the presence of mucosal telangiectasias that are fragile and prone to hemorrhage, a variety of endoscopic methods have been used to obliterate these vessels.

Lasers—Argon and neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers have been used to coagulate bleeding angiodysplasias in chronic radiation proctopathy. The potential benefit of Nd:YAG lasers were shown in a study from Mayo Clinic of 47 patients with hemorrhagic chronic radiation proctopathy despite previous medical treatment (98%) or bypass colostomy (6%) [41]. The median number of laser sessions was two (one to nine). Within a 3–6-month period after laser treatment, the number of patients with daily hematochezia decreased significantly (85–11%; $p < 0.001$), and the median hemoglobin level increased from 9.7 g/dL to 11.7 g/dL ($p < 0.001$). Six patients (12.8%) were not improved by laser treatment and two (4%) ultimately required surgical treatment for bleeding control. No deaths were reported. However, three patients (6%) developed complications including a patient with a rectovaginal fistula requiring rectosigmoid resection with end sigmoid colostomy.

Experience with argon laser has been published in a smaller study of 14 patients with bleeding from chronic radiation proctopathy [42]. A total of 51 procedures were described with a median of three procedures performed per patient, with two sessions required for initial control of bleeding. Ten patients (71%) required maintenance therapy with mean interval between maintenance sessions of 7 months. No immediate or late complications were reported in the study.

Bipolar and heater probe electrocoagulation—Bipolar and heater probe electrocoagulation (BiCap) are other endoscopic modalities that have been used in the treatment of hematochezia secondary to chronic radiation proctopathy that are widely available and inexpensive compared to lasers. The efficacy and safety of bipolar or heater probe endoscopic coagulation was evaluated in a prospective, randomized trial involving 21 patients with chronic recurrent hematochezia and anemia (after 12 months of medical therapy with corticosteroid or salicylate enemas) due to radiation-induced injury [43]. Patients were treated with either BiCap or heater probe therapy as needed. Rectal bleeding stopped within four treatment sessions. Compared to the 12 months of medical therapy, severe bleeding episodes diminished significantly for bipolar probe (75% vs 33%) and heater probe therapy (67% vs 11%). Mean hematocrit also rose significantly with both bipolar (38.2 vs 31.9) and heater probe (37.6 vs 28.4) treatments. Additionally, no serious complications were reported in the study.

Argon plasma coagulation—APC is a non-contact thermal coagulation procedure, in which electrical energy is transferred to the target tissue using ionized argon gas (argon plasma). Inert argon gas is pumped at a specified flow rate through a probe passed through the endoscope channel. The gas gets ionized by a high voltage current (earthed) producing thermal energy that heats the surface in a uniform manner to a depth of around 0.5–3 mm [44]. Thus, this technique coagulates superficial blood vessels without damaging deeper tissues or causing perforation.

APC causes regression of bleeding in 80−90% of the cases and improves diarrhea and tenesmus in 60 –75% of cases [44]. APC treatment, when available, represents the safest and most effective thermal contact method for chronic radiation proctopathy. However, it generally requires more than one treatment session to decrease or prevent bleeding. Table 15.3 shows all published studies on APC for chronic radiation proctopathy. In a study by Swan et al. [56], 50 patients with chronic radiation proctitis, 17 (34%) patients with grade A endoscopic severity, 23 (46%) grade B, and 10 (20%) grade C, received APC treatment. APC was applied at an average power of 50 W with flow rates between 1.4 and 2.0 L/min. The mean number of treatments required was 1.4 (range 1–3) with a 98% success rate. This included improvement in bleeding scores in all patients ($P < .001$). Complications were mainly short term and resolved spontaneously in 17 (34%) patients (proctalgia in 13 patients, rectal mucous discharge in 4, incontinence in 1, fever

Table 15.3 Overview on argon plasma coagulation (APC) use in chronic

Authors (year) (Ref.)	*N*	Requiring transfusion (%)	Settings (L/min)	Mean no. of APC sessions	Success rate (%)
Silva et al. (1999) [45]	28	53	50 W 1.5	2.9	93
Fantin et al. (1999) [46]	7	–	60 W 3.0	2.4	100
Tam et al. (2000) [47]	15	20	60 W 2.0	2.0	100
Kaassis et al. (2000) [48]	16	19	40 W 0.6	3.7	100
Tjandra & Sengupta (2001) [49]	12	33	40 W 1.5	2.0	83
Taieb et al. (2001) [50]	11	64	50 W 0.8–2	3.2	100
Villavicencio et al. (2002) [51]	21	19	45–50 W 1.2–2	1.7	95
Zinicola et al. (2003) [52]	14	21	65 W 2.0	1.7	86
Canard et al. (2003) [53]	30	17	30 ± 80 W 0.8 ± 2.0	2.3	87
Ben−Soussan et al. (2004) [54]	27	30	40 ± 50 W 0.8 ± 1.0	2.66	92
Karamanolis et al. (2009) [55]	56	16	40 W 2	2	89
Swan et al.(2010) [56]	50	–	50 W 1.4–2	1.4	98
López-Arce et al. (2010) [57]	19	26.3	40 ± 50 W 1–1.5	1.5	100
Sato et al. (2011) [58]	65	18.8	40 W 1.2	2.1	98.5

L liter, *W* watts

in one, and bleeding in 1 patient). One patient had an asymptomatic rectal stricture on subsequent screening colonoscopy that did not require dilation.

Sato et al. [58], studied 65 patients with chronic radiation proctopathy over a 10-year period. Seven patients (10.8%) had grade A (mild), 41 (63.1%) had grade B (moderate), and 17 (26.2%) had grade C (severe) proctopathy. The study utilized APC at 40 W current, 1.2-L/min gas flow rate, and 2-s applications. The treatment success rate was 98.5% after an average of 2.1 APC sessions. The median clinical score for rectal bleeding was significantly decreased after APC ($P<0.0001$), and the hemoglobin level was significantly increased ($P<0.0001$). Importantly, APC was well tolerated, with no serious side effects or complications. In the follow-up period, only 4 patients (6.3%) had minor recurrent rectal bleeding and 60 (93.8%) remained in remission.

The most common procedure-related symptom is of anal or rectal pain which is mild and self-limiting [44]. It is most likely to occur following APC treatment near the dentate line. Major complications from APC are rare. The frequency of perforation was 0.27% in a study of 1062 patients [59]. Colonic explosion is another rare but preventable complication of APC, with seven published case reports involving eight patients in nine separate incidents of colonic explosion reported. Four of these occurred during treatment of chronic radiation proctopathy [60]. Bowel preparation with an oral polyethylene glycol-based preparation is essential before performing an APC to prevent these explosions and should also be used for any follow-up APC procedures in the same patient [60]. Treatment-related ulcers are seen in 52% of the patients. One investigator has suggested avoiding these ulcer sites during repeat APC sessions [61]. Our practice is to discontinue APC in the setting of deep rectal ulcerations. These patients may be candidates for carefully applied formalin dab therapy if ongoing bleeding from remaining telangiectasias occurs or HBO treatments if ulcers are symptomatic and do not heal. Clinically, retinyl palmitate probably also has a role in these patients. APC treatment around radiation-induced rectal strictures may worsen the severity of the stricture as the treated mucosa heals and hence may be inappropriate in this setting. Rectovaginal fistulas have also been reported as a rare and late complication of APC in this patient group [44].

Cryoablation—Cryoablation is a technique involving noncontact application of liquid nitrogen or carbon dioxide gas to tissue for superficial ablation that has been used in the treatment of esophageal high-grade dysplasia and early cancer. A recent prospective case-series pilot study assessed response and tolerability to cryo-ablation

Table 15.4 Pharmacological methods for prevention of radiation enteropathy and proctopathy

Regimen	Mechanism	Clinical trial
Amifostine	Active metabolite WR-1065 scavenges radiation-induced free radicals	Yes
5-Aminosalicylates	Anti-inflammatory	Yes
Octreotide	Reduced secretion of pancreatic enzymes	No
Selenium	Antioxidant role via increased biosynthesis of the different glutathione peroxidase and thioredoxin reductase isozymes	Yes
Prostaglandin E2 analogs	Trophic effect on enterocytes	No
Sucralfate	Angiogenesis mediated via bFGF and increased mucosal glutathione	No
Glutamine	Trophic to enterocytes	No
TGF-beta type II receptor fusion protein	Modulation of fibrogenic cytokine TGF-beta type I involved in radiation-induced fibrosis	No

therapy in ten patients with chronic radiation proctopathy [62]. Endoscopic severity (measured by rectal telangiectasia density) improved from 2.7 to 1.7 ($P=0.004$). Overall subjective clinical scores on RPSAS (scale described previously) improved from 27.7 to 13.6 ($P=0.003$). One complication of cecal perforation due to gaseous over-distention decompression tube failure was seen. Additional controlled trials to establish the safety and efficacy of cryoablation are advised.

In patients with mild symptoms of obstructive defecation from chronic radiation proctopathy, stool softeners have been recommended. If these are not helpful, balloon or Savary-Gilliard dilation may be effective in patients with obstructive symptoms from distal colonic strictures that are short and are present in nonangulated areas of the colon or rectum [63]

Prevention

Apart from improvements in the radiation technique and dosing, a number of other preventive strategies to decrease the incidence and severity of chronic radiation proctopathy have been investigated (Table 15.4). One of the major concerns in this field is the development of agents that are radioprotective to normal tissue without directly enhancing tumor activity or diminishing the effects of radiation therapy.

bFGF basic fibroblast growth factor, *TGF* transforming growth factorAmifostine—Amifostine is a prodrug that undergoes intracellular dephosphorylation by alkaline phosphatase to the active metabolite WR-1065. It appears to be selective in its entry in nonmalignant cells and attenuates cell injury from radiation by scavenging of radiation-induced free radicals [64]. It is one of the most thoroughly studied radioprotective agents. Evidence for efficacy in the reduction of acute radiation-induced GI toxicity with monitoring for of tumor protective effects was investigated in a prospective, randomized trial of 205 patients with pelvic malignancies [64]. The participants were randomized to receive radiotherapy with or without amifostine (administered at 340 mg/m2 i.v., 15 min before radiotherapy). A significant reduction in Radiation Therapy Oncology Group/European Organization Research and Treatment of Cancer (RTOG/EORTC) grade 2–3 acute lower GI tract toxicities occurred in the amifostine group ($p<0.05$, weeks 3–7). More importantly, no statistically significant difference between the two groups was observed in terms of response at 6 weeks after radiotherapy completion (complete response plus partial response was 98.3% in the amifostine arm vs 96.8% in the control group). Amifostine infusions were well tolerated, with only moderate hypotension occurring in two patients and moderate nausea in one patient. No long-term toxicities related to amifostine infusion were reported during the follow-up period.

In another prospective, randomized trial of 100 patients with inoperable, unresectable, or recurrent adenocarcinoma of the rectum, patients were randomized to receive radiotherapy with

or without amifostine (340 mg/m^2 i.v., 15 min before RT) [65]. No moderate or severe normal pelvic tissue late effects were seen in the 34 evaluable patients in the amifostine group whereas 5 of 37 evaluable patients in the control group exhibited late effects of moderate or severe degree ($P=0.03$). More convenient and less expensive routes of administration of amifostine have also been tested. In a study by Kouloulias et al. [66], patients were randomized to receive amifostine, either as a 1500 mg dose in 40 mL enema ($n=27$) or a 500 mg subcutaneous dose ($n=26$) before irradiation. Intrarectal amifostine demonstrated significantly lower incidence of RTOG/EORTC grades I–II rectal radiation morbidity (11 % vs 42 %, $p=0.04$) 1–2 days after radiotherapy completion but had inferior results for urinary toxicity (48 % vs 15 %, $p=0.03$). Rectal amifostine was well tolerated without any toxicity while World Health Organization (WHO) Grade 1 nausea was noted in three (11 %) of the patients who received amifostine via subcutaneous route, lasting nearly 6 h after amifostine injection. Four patients (15 %) in this group also complained of severe asthenia (WHO Grades 2–3) that was cumulative, occurring from the 4th to the 20th day of amifostine injection. This symptom resulted in discontinuation for 24 h until the symptoms of asthenia had regressed. As a result of these and other trials, the updated clinical practice guidelines developed by the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology suggest that amifostine in a dose $\geq$340 mg/m^2 may prevent acute and chronic radiation proctopathy in patients undergoing standard-dose radiotherapy for rectal cancer [67].

Sulfasalazine and balsalazide —5-Amino salicylic acid may have a role in preventing or reducing acute radiation proctopathy. Twenty-seven prostate cancer patients receiving external beam radiotherapy were administered 2.25 g of balsalazide or an identical-appearing placebo twice daily beginning 5 days before radiotherapy and continuing for 2 weeks after completion [68]. A symptom index was calculated for individual toxicity consisting of the toxicity's numeric grade multiplied by the number of days it was experienced, and summed throughout the course of radiotherapy. All toxicities were lower with balsalazide, with the exception of nausea and vomiting seen in three patients on balsalazide and two on placebo. Scoring of acute symptoms showed statistical improvement, with a mean proctitis index of 35.3 in balsalazide patients and 74.1 in placebo patients ($p=0.04$).

Results from controlled clinical trials evaluating mesalazine or sulfasalazine in the prevention of acute radiation enteropathy have been discordant. In a randomized double-blind placebo-controlled trial involving 87 patients receiving pelvic radiotherapy, diarrhea occurred in 55 % and 86 % of the sulfasalazine and placebo groups, respectively ($P=0.001$) [69]. However, another randomized double-blind placebo-controlled trial evaluating mesalazine in 153 patients receiving pelvic radiotherapy failed to show an improvement in diarrheal symptoms seen in 69 % of the mesalazine and 66 % of the placebo group, $P=0.22$ [70]. Nonetheless, the European Society for Medical Oncology guidelines for management of oral and GI mucositis published in 2009 recommends the use of 500 mg sulfasalazine orally twice daily to reduce the incidence and severity of radiation-induced enteropathy in patients receiving external beam radiotherapy to the pelvis [71].

A number of other agents have been investigated in animal models or preliminary clinical studies. Pancreatic enzymes have been shown to exacerbate acute intestinal radiation toxicity in animal models [72]. Reducing pancreatic secretion with a synthetic somatostatin receptor analog such as octreotide was thought to be a strategy that may confer a dose-dependent protection against delayed small bowel radiation toxicity and ameliorate radiation fibrosis predominantly by reducing acute mucosal injury [73]. This was evaluated in a randomized, double-blinded, placebo-controlled trial of 125 patients receiving pelvic radiotherapy. Patients were randomized to receive octreotide (100 mcg, administered subcutaneously on day 1, followed by depot octreotide, 20 mg, administered intramuscularly on days 2 and 29; $n=62$) or to receive a placebo injection ($n=63$) [74]. Grade 0, 1, 2, and 3 diarrhea

were observed in similar percentages of patients in both groups ($P=0.64$). Some other symptoms such as nocturnal bowel movements (70% vs 45%; $P=0.004$) and bleeding with bowel movements (57% vs 35%; $P=0.01$) were worse in the octreotide arm. Hence, octreotide injection is not recommended for prevention of diarrhea during pelvic radiation therapy.

Selenium supplementation was studied in a small multicenter phase III trial involving 81 patients receiving pelvic radiotherapy for uterine and cervical cancer and with initial selenium concentrations of less than 84 mcg/L [75]. The participants were randomized before radiotherapy to receive 500 mcg of selenium (sodium selenite) by mouth on the days of radiotherapy ($n=39$) and 300 mcg of selenium on the days without radiotherapy or to receive no supplement ($n=42$) during the radiotherapy. A significantly lower incidence of CTC (version 2) Grade 2 or higher diarrhea was seen in the selenium supplementation group compared with the control group (20.5% vs 44.5%; $P=0.04$). A larger controlled trial to confirm these findings was advised before definite recommendations can be made for prophylactic selenium supplementation to reduce acute radiation enteropathy.

Prostaglandin E2 and prostaglandin analogs displayed initial promise in radiation protection in animal studies [76]. However, in a phase III randomized, placebo-controlled, double-blind study of 100 patients who underwent radiotherapy for prostate cancer, no differences were found in proctitis symptom onset or duration. In addition, significantly more patients receiving the prostaglandin analogue misoprostol experienced rectal bleeding compared to placebo ($p=0.03$) [77]. Sucralfate has also been evaluated for prophylaxis against acute radiation enteropathy and proctopathy. A meta-analysis failed to show a beneficial role for sucralfate either orally or as enema as a prophylaxis for acute radiation proctopathy [78]. Additionally, a double-blind, placebo-controlled, randomized trial evaluated 338 patients receiving definitive radiotherapy for prostate cancer randomized to receive either 3 g of oral sucralfate suspension or placebo twice daily, failed to demonstrate a statistically significant reduction in the incidence of late rectal toxicity in patients randomized to receive sucralfate [79].

Enterotrophic strategies to increase the resistance of the bowel to radiation injury and/or enhance its capacity for recovery for protection against radiation injury have focused on glutamine. However, a phase III, randomized, double-blind study, involving 129 patients failed, to show any beneficial effect for glutamine given as 4 g orally, twice a day, beginning with the first or second day of RT and continuing for 2 weeks after RT. No difference was seen in diarrhea levels (maximum CTC grade of diarrhea, incidence of diarrhea, and average diarrhea score) [80]. Finally, preliminary animal models have identified a putative role for modulation of the fibrogenic cytokine transforming growth factor (TGF) beta 1 in ameliorating radiation enteropathy. Recombinant TGF-beta type II receptor fusion protein has been shown to function as a "scavenger" of active TGF-beta 1, thus suggesting a possible future therapeutic tool. This remains an ongoing area of investigation [81].

References

1. Hauer-Jensen M, Wang J, Denham JW. Bowel injury: current and evolving management strategies. Semin Radiat Oncol. 2003;13:357–71.
2. Henriksson R, Franzen L, Littbrand B. Effects of sucralfate on acute and late bowel discomfort following radiotherapy of pelvic cancer. J Clin Oncol. 1992;10:969–75.
3. Berk RN, Seay DG. Cholerheic enteropathy as a cause of diarrhea and death in radiation enteritis and its prevention with cholestyramine. Radiology. 1972;104:153–6.
4. Mennie AT, Dalley VM, Dinneen LC, Collier HO. Treatment of radiation-induced gastrointestinal distress with acetylsalicylate. The Lancet. 1975;2:942–3.
5. Sekhon S. Chronic radiation enteritis: women's food tolerances after radiation treatment for gynecologic cancer. J Am Diet Assoc. 2000;100(8):941–3.
6. Jain G, Scolapio J, Wasserman E, Floch MH. Chronic radiation enteritis: a ten-year follow-up. J Clin Gastroenterol. 2002;35(3):214–7.
7. Scolapio JS, Ukleja A, Burnes JU, Kelly DG. Outcome of patients with radiation enteritis treated with home parenteral nutrition. Am J Gastroenterol. 2002; 97(3):662–6.

8. Gavazzi C, Bhoori S, Lovullo S, Cozzi G, Mariani L. Role of home parenteral nutrition in chronic radiation enteritis. Am J Gastroenterol. 2006;101(2):374–9.
9. Yeoh EK, Horowitz M, Russo A, Muecke T, Robb T, Chatterton BE. Gastrointestinal function in chronic radiation enteritis-effects of loperamide-N-oxide. Gut. 1993;34(4):476–82.
10. Goldstein F, Khoury J, Thornton JJ. Treatment of chronic radiation enteritis and colitis with salicylazosulfapyridine and systemic corticosteroids. A pilot study. Am J Gastroenterol. 1976;65(3):201–8.
11. VAN UNNIKA. Inhibition of toxin production in clostridium perfringens in vitro by hyperbaric oxygen. Antonie Van Leeuwenhoek. 1965;31:181–6.
12. Hill GB, Osterhout S. Experimental effects of hyperbaric oxygen on selected clostridial species. I. In-vitro studies. J Infect Dis. 1972;125(1):17–25.
13. Marx RE, Ehler WJ, Tayapongsak P. Relationship of oxygen dose to angiogenesis induction in irradiated tissue. Am J Surg. 1990;160:519–24.
14. Neurath MF, Branbrink A, Meyer zumBKH, Lohse AW. A new treatment for severe malabsorption due to radiation enteritis. The Lancet. 1996;347(9011):1302.
15. Huddy JE, Patel P, Johnson MW, Hamilton-Farrell MR, Ede RJ, Sanderson JD. Hyperbaric oxygen as a treatment for malabsorption in a radiation-damaged short bowel. Eur J Gastroenterol Hepatol. 2006;18(6):685–8.
16. Gouello J, Bouachour G, Person B, Ronceray J, Cellier P, Alquier P Intérêt de l'oxygènothérapie hyperbare dans la pathologie digestive post-radique: 36 observations. La Presse médicale. 1999;28(20):1053–57.
17. Feldmeier JJ, Heimbach RD, Davolt DA, Court WS, Stegmann BJ, Sheffield PJ. Hyperbaric oxygen an adjunctive treatment for delayed radiation injuries of the abdomen and pelvis. Undersea Hyperb Med. 1996;23(4):205–13.
18. Marshall GT, Thirlby RC, Bredfeldt JE, Hampson NB. Treatment of gastrointestinal radiation injury with hyperbaric oxygen. Undersea Hyperb Med. 2007;34(1):35–42.
19. Leach RM, Rees PJ, Wilmshurst P. Hyperbaric oxygen therapy. BMJ. 1998;317(7166):1140–3.
20. Vernia P, Fracasso PL, Casale V, Villotti G, Marcheggiano A, Stigliano V, et al. Topical butyrate for acute radiation proctitis: randomised, crossover trial. The Lancet. 2000;356(9237):1232–5.
21. Hille A, Herrmann MK, Kertesz T, Christiansen H, Hermann RM, Pradier O, et al. Sodium butyrate enemas in the treatment of acute radiation-induced proctitis in patients with prostate cancer and the impact on late proctitis. A prospective evaluation. Strahlenther Onkol. 2008;184(12):686–92.
22. 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(205):40–53.
23. 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.
24. Sandor Z, Nagata M, Kusstatscher S, Szabo S. Stimulation of mucosal glutathione and angiogenesis: new mechanisms of gastroprotection and ulcer healing by sucralfate. Scand J Gastroenterol Suppl. 1995;210:19–21.
25. Kochhar R, Patel F, Dhar A, Sharma SC, Ayyagari S, Aggarwal R, et al. Radiation-induced proctosigmoiditis. Prospective, randomized, double-blind controlled trial of oral sulfasalazine plus rectal steroids versus rectal sucralfate. Dig Dis Sci. 1991;36(1):103–7.
26. Kochhar R, Sriram PV, Sharma SC, Goel RC, Patel F. Natural history of late radiation proctosigmoiditis treated with topical sucralfate suspension. Dig Dis Sci. 1999;44(5):973–8.
27. Sasai T, Hiraishi H, Suzuki Y, Masuyama H, Ishida M, Terano A. Treatment of chronic post-radiation proctitis with oral administration of sucralfate. Am J Gastroenterol. 1998;93(9):1593–5.
28. Cavcić J, Turcić J, Martinac P, Jelincić Z, Zupancić B, Panijan-Pezerović R, et al. Metronidazole in the treatment of chronic radiation proctitis: clinical trial. Croat Med J. 2000;41(3):314–8.
29. 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(4):1080–4.
30. Ehrenpreis ED, Jani A, Levitsky J, Ahn J, Hong J. A prospective, randomized, double-blind, placebo-controlled trial of retinol palmitate (vitamin A) for symptomatic chronic radiation proctopathy. Dis Colon Rectum. 2005;48(1):1–8.
31. Dall'Era MA, Hampson NB, Hsi RA, Madsen B, Corman JM. Hyperbaric oxygen therapy for radiation induced proctopathy in men treated for prostate cancer. Urol. 2006;176(1):87–90.
32. Clarke RE, Tenorio LM, Hussey JR, Toklu AS, Cone DL, Hinojosa JG, et al. 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(1):134–43.
33. de Parades V, Etienney I, Bauer P, Bourguignon J, Meary N, Mory B, et al. Formalin application in the treatment of chronic radiation-induced hemorrhagic proctitis-an effective but not risk-free procedure: a prospective study of 33 patients. Dis Colon Rectum. 2005;48(8):1535–41.
34. Haas EM, Bailey HR, Farragher I. Application of 10% formalin for the treatment of radiation-induced hemorrhagic proctitis. Dis Colon Rectum. 2007;50(2):213–7.
35. Luna-Pérez P, Rodríguez-Ramírez SE. Formalin instillation for refractory radiation-induced hemorrhagic proctitis. J Surg Oncol. 2002;80(1):41–4.
36. Myers JA, Mall J, Doolas A, Jakate SM, Saclarides TJ. Absorption kinetics of rectal formalin instillation. World J Surg. 1997;21(8):886–9.

37. Pinto A, Fidalgo P, Cravo M, Midões J, Chaves P, Rosa J, et al. Short chain fatty acids are effective in short-term treatment of chronic radiation proctitis: randomized, double-blind, controlled trial. Dis Colon Rectum. 1999;42(6):788–95.
38. Pilepich MV, Paulus R, Clair W St, Brasacchio RA, Rostock R, Miller RC. Phase III study of pentosan-polysulfate (PPS) in treatment of gastrointestinal tract sequelae of radiotherapy. Am J Clin Oncol. 2006;29(2):132–7.
39. Baum CA, Biddle WL, Miner PB Jr. Failure of 5-aminosalicylic acid enemas to improve chronic radiation proctitis. Dig Dis Sci. 1989;34(5):758–60.
40. Wurzer H, Schafhalter-Zoppoth I, Brandstätter G, Stranzl H. Hormonal therapy in chronic radiation colitis. Am J Gastroenterol. 1998;93(12):2536–8.
41. Viggiano TR, Zighelboim J, Ahlquist DA, Gostout CJ, Wang KK, Larson MV. Endoscopic Nd: YAG laser coagulation of bleeding from radiation proctopathy. Gastrointest Endosc. 1993;39(4):513–7.
42. Taylor JG, DiSario JA, Buchi KN. Argon laser therapy for hemorrhagic radiation proctitis: long-term results. Gastrointest Endosc. 1993;39(5):641–4.
43. 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(1):20–5.
44. Postgate A, Saunders B, Tjandra J, Vargo J. Argon plasma coagulation in chronic radiation proctitis. Endoscopy. 2007;39:361–5.
45. Silva RA, Correia AJ, Dias LM, Viana HL, Viana RL. Argon plasma coagulation therapy for hemorrhagic radiation proctosigmoiditis. Gastrointest Endosc. 1999;50:221–4.
46. Fantin AC, Binek J, Suter WR, Meyenberger C. Argon beam coagulation for treatment of symptomatic radiation−induced proctitis. Gastrointest Endosc. 1999;49:515–8.
47. Tam W, Moore J, Schoeman M. Treatment of radiation proctitis with argon plasma coagulation. Endoscopy. 2000;32:667–72.
48. Kaassis M, Oberti E, Burtin P, Boyer J. Argon plasma coagulation for the treatment of hemorrhagic radiation proctitis. Endoscopy. 2000;32(9):673–6.
49. Tjandra JJ, Sengupta S. Argon plasma coagulation is effective in the treatment of refractory radiation proctitis. Dis Colon Rectum. 2001;44:1759–65.
50. Taïeb S, Rolachon A, Cenni JC, Nancey S, Bonvoisin S, Descos L, et al. Effective use of argon plasma coagulation in the treatment of severe radiation proctitis. Dis Colon Rectum. 2001;44(12):1766–71.
51. Villavicencio RT, Rex DK, Rahmani E. Efficacy and complications of argon plasma coagulation for hematochezia related to radiation proctopathy. Gastrointest Endosc. 2002;55(1):70–4.
52. Zinicola R, Rutter MD, Falasco G, Brooker JC, Cennamo V, Contini S, et al. Haemorrhagic radiation proctitis: endoscopic severity may be useful to guide therapy. Int J Colorect Dis. 2003;18:439–44.
53. 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;27:455–9.
54. 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(12):1315–8.
55. Karamanolis G, Triantafyllou K, Tsiamoulos Z, Polymeros D, Kalli T, Misailidis N, et al. Argon plasma coagulation has a long-lasting therapeutic effect in patients with chronic radiation proctitis. Endoscopy. 2009;41(6):529–31.
56. 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(1):150–4.
57. López-Arce G, Téllez-Avila FI, García-Osogobio S, Chavez-Tapia NC, Barahona-Garrido J, Barreto-Zúñiga R, et al. Endoscopic treatment with argon plasma coagulation in postradiation proctopathy. Int J Colorectal Dis. 2010;25(7):895–8.
58. Sato Y, Takayama T, Sagawa T, Hirakawa M, Ohnuma H, Miyanishi K, et al. Argon plasma coagulation treatment of hemorrhagic radiation proctopathy: the optimal settings for application and long-term outcome. Gastrointest Endosc. 2011;73(3):543–9.
59. Grund KE, Zindel C, Farin G. Argon plasma coagulation (APC) in flexible endoscopy. Experience with 2193 applications in 1062 patients [abstract]. Gastroenterology. 1998;114:A603.
60. Deepak P, Devi R, Sifuentes H, Ehrenpreis ED. Use of polyethylene glycol-based colonoscopy preparations before rectal argon plasma coagulation: lessons still to be learned by practicing gastroenterologists. J Clin Gastroenterol. 2012;46(9):803–4.
61. 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(4):519–25.
62. Hou JK, Abudayyeh S, Shaib Y. Treatment of chronic radiation proctitis with cryoablation. Gastrointest Endosc. 2011;73(2):383–9.
63. Triadafilopoulos G, Sarkisian M. Dilatation of radiation-induced sigmoid stricture using sequential Savary-Guilliard dilators. A combined radiologic-endoscopic approach. Dis Colon Rectum. 1990;33(12):1065–7.
64. Athanassiou H, Antonadou D, Coliarakis N, Kouveli A, Synodinou M, Paraskevaidis M, et al. Protective effect of amifostine during fractionated radiotherapy in patients with pelvic carcinomas: results of a randomized trial. Int J Radiat Oncol Biol Phys. 2003;56(4):1154–60.
65. Liu T, Liu Y, He S, Zhang Z, Kligerman MM. Use of radiation with or without WR-2721 in advanced rectal cancer. Cancer. 1992;69(11):2820–5.

66. Kouloulias VE, Kouvaris JR, Pissakas G, Mallas E, Antypas C, Kokakis JD, et al. Phase II multicenter randomized study of amifostine for prevention of acute radiation rectal toxicity: topical intrarectal versus subcutaneous application. Int J Radiat Oncol Biol Phys. 2005;62(2):486–93.
67. Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer. 2007;109(5):820–31.
68. Jahraus CD, Bettenhausen D, Malik U, Sellitti M, St Clair WH. Prevention of acute radiation-induced proctosigmoiditis by balsalazide: a randomized, double-blind, placebo controlled trial in prostate cancer patients. Int J Radiat Oncol Biol Phys. 2005;63(5):1483–7.
69. Kiliç D, Egehan I, Ozenirler S, Dursun A. Double-blinded, randomized, placebo-controlled study to evaluate the effectiveness of sulphasalazine in preventing acute gastrointestinal complications due to radiotherapy. Radiother Oncol. 2000;57(2):125–9.
70. Resbeut M, Marteau P, Cowen D, Richaud P, Bourdin S, Dubois JB, et al. A randomized double blind placebo controlled multicenter study of mesalazine for the prevention of acute radiation enteritis. Radiother Oncol. 1997;44(1):59–63.
71. Peterson DE, Bensadoun RJ, Roila F. ESMO guidelines working group. Management of oral and gastrointestinal mucositis: ESMO clinical recommendations. Ann Oncol. 2009;20 (Suppl 4):174–7.
72. Sokol A, Lipson L, Morgenstern L, Hiatt N. Protection against lethal irradiation injury by pancreatic enzyme exclusion. Surg Forum. 1967;18:387–9.
73. Wang J, Zheng H, Hauer-Jensen M. Influence of short-term octreotide administration on chronic tissue injury, transforming growth factor β (TGF-β) overexpression, and collagen accumulation in irradiated rat intestine. J Pharmacol Exp Ther. 2001;297(1):35–42.
74. Martenson JA, Halyard MY, Sloan JA, Proulx GM, Miller RC, Deming RL, et al. Phase III, double-blind study of depot octreotide versus placebo in the prevention of acute diarrhea in patients receiving pelvic radiation therapy: results of North Central Cancer Treatment Group N00CA. J Clin Oncol. 2008;26(32):5248–53.
75. Muecke R, Schomburg L, Glatzel M, Berndt-Skorka R, Baaske D, Reichl B, et al. Multicenter, phase 3 trial comparing selenium supplementation with observation in gynecologic radiation oncology. Int J Radiat Oncol Biol Phys. 2010;78(3):828–35.
76. Keelan M, Walker K, Cheeseman CI, Thomson AB. Two weeks of oral synthetic E2 prostaglandin (enprostil) improves the intestinal morphological but not the absorptive response of the rat to abdominal irradiation. Digestion. 1992;53(1–2):101–7.
77. Hille A, Schmidberger H, Hermann RM, Christiansen H, Saile B, Pradier O, et al. A phase III randomized, placebo-controlled, double-blind study of misoprostol rectal suppositories to prevent acute radiation proctitis in patients with prostate cancer. Int J Radiat Oncol Biol Phys. 2005;63(5):1488–93.
78. Hovdenak N, Sørbye H, Dahl O. Sucralfate does not ameliorate acute radiation proctitis: randomised study and meta-analysis. Clin Oncol (R Coll Radiol). 2005;17(6):485–91.
79. Kneebone A, Mameghan H, Bolin T, Berry M, Turner S, Kearsley J, et al. Effect of oral sucralfate on late rectal injury associated with radiotherapy for prostate cancer: a double-blind, randomized trial. Int J Radiat Oncol Biol Phys. 2004;60(4):1088–97.
80. Kozelsky TF, Meyers GE, Sloan JA, Shanahan TG, Dick SJ, Moore RL, et al. Phase III double-blind study of glutamine versus placebo for the prevention of acute diarrhea in patients receiving pelvic radiation therapy. J Clin Oncol. 2003;21(9):1669–74.
81. Zheng H, Wang J, Koteliansky VE, Gotwals PJ, Hauer-Jensen M. Recombinant soluble transforming growth factor-b type II receptor ameliorates radiation enteropathy in the mouse. Gastroenterology. 2000;119(5):1286–96.