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Pelvic radiation disease: Updates on treatment options

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Abstract

Pelvic cancers are among the most frequently diagnosed neoplasms and radiotherapy represents one of the main treatment options. The irradiation field usually encompasses healthy intestinal tissue, especially of distal large bowel, thus inducing gastrointestinal (GI) radiation-induced toxicity. Indeed, up to half of radiation-treated patients say that their quality of life is affected by GI symptoms (*e.g.*, rectal bleeding, diarrhoea). The constellation of GI symptoms - from transient to long-term, from mild to very severe - experienced by patients who underwent radiation treatment for a pelvic tumor have been comprised in the definition of pelvic radiation disease (PRD). A correct and evidence-based therapeutic approach of patients experiencing GI radiation-induced toxicity is mandatory. Therapeutic non-surgical strategies for PRD can be summarized in two broad categories, *i.e.*, medical and endoscopic. Of note, most of the studies have investigated the management of radiation-induced rectal bleeding. Patients with clinically significant bleeding (*i.e.*, causing chronic anemia) should firstly be considered for medical management (*i.e.*, sucralfate enemas, metronidazole and hyperbaric oxygen); in case of failure, endoscopic treatment should be implemented. This latter should be considered the first choice in case of acute, transfusion requiring, bleeding. More well-performed, high quality studies should be performed, especially the role of medical treatments should be better investigated as well as the comparative studies between endoscopic and hyperbaric oxygen treatments.

Key words: Pelvic radiation disease; Radiation-induced proctopathy; Radiotherapy; Gastrointestinal toxicity; Sucralfate; Metronidazole; Probiotics; Argon plasma coagulation; Hyperbaric oxygen; Formalin

Core tip: Radiotherapy is frequently employed as part of the multimodal treatment of pelvic cancers. Despite recent advances in irradiation techniques, acute and late- onset radiation-induced gastrointestinal toxicity, also known as pelvic radiation disease, is still being frequently reported. This review provides an up-to-

date summary on medical and endoscopic approaches that have been evaluated with treating intent, focusing on the best available evidence, primarily randomized controlled studies.

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INTRODUCTION

Pelvic cancers are among the most frequently diagnosed neoplasms[1]. The employment of radiation therapy as part of a multidisciplinary treatment for pelvic malignancy has progressively increased in recent years[2], as it is estimated that over 200000 patients in the United States receive pelvic or abdominal radiation therapy annually. The irradiation field usually encompasses healthy intestinal tissue, especially of distal large bowel, thus inducing gastrointestinal (GI) radiation-induced toxicity. Indeed, up to half of radiation-treated patients say that their quality of life is affected by gastrointestinal symptoms[3]. Recently, the constellation of gastrointestinal symptoms - from transient to long-term, from mild to very severe - experienced by patients who underwent radiation treatment for a pelvic tumor have been comprised in the definition of pelvic radiation disease (PRD)[3]. Radiation toxicity is defined as acute when occurring during radiotherapy or within 3 mo, while it is considered as chronic when developing after longer period of time. Among the most frequently reported symptoms are diarrhea, urgency, rectal bleeding and fecal incontinence[4].

The type of irradiation technique has been recognized as an influential factor for the development of PRD[5]. It is important to notice that even the most recent radiation procedures, such as intensity-modulated radiotherapy, have reduced but not completely annulled the occurrence of GI radiation-related toxicity[6]. Moreover, the prolonged survival of this category of patients will undoubtedly increase the risk of developing PRD over time. Thus, a correct and evidence-based therapeutic approach of patients experiencing gastrointestinal radiation-induced toxicity is mandatory. Therapeutic non-surgical strategies for PRD can be summarized in two broad categories, *i.e.*, medical and endoscopic. Over years, a number of medical treatments have been investigated, such as aminosalicylates, sucralfate, antibiotics, probiotics, steroids and hyperbaric oxygen therapy. Endoscopic treatments have been explored too, including argon plasma coagulation, formaline application, radiofrequency, criotherapy and band ligation.

In the current review, we provide a critical appraisal of the efficacy of the treatment options for radiation-induced gastrointestinal toxicity.

Pathogenesis

The occurrence and severity of radiation-induced gastrointestinal toxicity depends upon several factors. Therapy-related factors include radiation dose, volume of irradiated bowel, time- and dose-fractioning parameters and concomitant employment of chemotherapy. Patient-related factors include smoking, body mass index, previous abdominal surgery and comorbidities like inflammatory bowel disease, diabetes and collagen vascular disease[7-13].

Traditionally, the development of radiation enteropathy was explained through the "target cell" theory, which addressed early pathology to the epithelial injury, while fibroblast and endothelial cell damage was accounted for late-onset harm[14]. In recent years, the above-mentioned theory has been questioned, and other factors have been taken into account. For instance, the enteric nervous system is the second largest nervous system of human body, and it has been pointed out as capable to regulate radiation enteropathy development[15]. It has also been demonstrated that the gut microbiota, consisting of about 100 trillion bacteria, influences radiation-induced damage[16]. Thus, the understanding of PRD pathogenesis has gone far beyond the single "target cell" concept, and considers intestinal toxicity as the result of multiple interactions between epithelial injury, gut microvasculature, enteric nervous system, and gut microbiota[17].

Acute and chronic gastrointestinal toxicity have a different pathogenesis[18]. Indeed, acute PRD is due to an acute inflammatory response, whilst chronic, late-onset disease is mainly mediated by vascular sclerosis and fibrosis[19]. However, acute and chronic radiation toxicities are not independent events, as it is underlined by the consequential late effect theory: indeed, late injury is more likely to develop when severe acute toxicity exists[20,21]. Recent studies have added complexity to these models[17], however a deeper discussion on the pathological basis of PRD is beyond the purpose of this review and we invite to consider for this purpose the review by Hauer-Jensen *et al*[17].

Treatment options

Medical treatment, hyperbaric oxygen therapy and endoscopic approaches represent the mainstay for treating pelvic radiation-induced disease. However, the existing evidence on such approaches for treating PRD cannot be judged as of high quality, due to few and low-quality randomized controlled trials (RCTs), high clinical and methodological heterogeneity, small sample sizes and short periods of follow-up[22].

MEDICAL TREATMENT

Medical therapy should represent the first step in the management of radiation-induced pelvic radiation disease. Over years, a number of medical treatments

Table 1 Medical strategies for treating pelvic radiation disease

Medical treatments	Acute PRD	Chronic PRD	Notes
Topical sucralfate	N	Y	Twice-daily enema with two 1 g sucralfate tablets mixed with 4.5 mL of water is effective for chronic rectal bleeding
Metronidazole	N	Y	3 × 400 mg/d of metronidazole for up to 12 wk is effective for chronic rectal bleeding and diarrhea
Probiotics	Y	N	3 sachets/d of *Lactobacillus rhamnosus* for at least 1 wk is effective for acute diarrhea
Mesalazine	N	N	No recent RCTs available; one prospective study showed that combined oral and topic mesalazine was effective for chronic rectal bleeding
Corticosteroids	N	N	RCTs have not shown a substantial improvement with steroids administration
Hyperbaric oxygen	N	Y	At least 30 sessions (up to 100) are effective for chronic rectal bleeding not responding to medical treatment

Y: Evidence supports treatment; N: Evidence does not support treatment; PRD: Pelvic radiation disease; RCT: Randomized controlled trial.

have been investigated, such as aminosalicylates, sucralfate, antibiotics, probiotics, steroids and hyperbaric oxygen therapy (Table 1).

Radiation-induced injury has been misleadingly referred to as *proctitis,* though inflammation has a non-central role in the pathogenesis of the disease. Thus, anti-inflammatory agents (steroids and 5-aminosalycilic acid) have traditionally been proposed as first-line treatment, with inconsistent results confirmed by a recent systematic review[23]. In fact, only sucralfate and metronidazole have clearly shown to be effective for treating symptoms of PRD, and the role of probiotics is supported by one RCT only.

Sucralfate

Rationale: Sucralfate is an alkaline aluminum hydroxide of sulfated sucrose. The rationale for the administration of sucralfate in the treatment of PRD lies on its supposed property to protect mucosa by forming a viscous superficial coating and to stimulate mucosal healing by its angiogenic action[24,25].

Evidences: According to published prospective studies - including one small, non-placebo controlled randomized controlled trial - topical sucralfate is effective in the treatment of PRD, as it significantly reduces the entity of rectal bleeding[26-29]. Indeed, patients experiencing symptoms improvement ranged from 73% to 100% of considered cohorts, after a follow-up period between four and six weeks. However, when surveillance interval was expanded, symptoms recurred in 10%-20% of patients[27,28]. Oral sucralfate was evaluated by one randomized, placebo-controlled trial and did not show to improve symptoms of PRD when added to endoscopic argon plasma coagulation[30].

Based on the available evidence, topical administration of sucralfate should be considered as one of the first-line treatments of radiation-induced rectal bleeding. The topical administration is the only way of assumption that showed to be effective for PRD[26,27,29]. Sucralfate can be administered twice daily as a retention enema prepared by patients themselves, using two 1 g sucralfate tablets mixed with 4.5 mL of water in an enema applicator and producing a low-volume paste[29].

Metronidazole

Rationale: Metronidazole is a bactericidal agent that kills anaerobic and microaerophilic bacteria, which contribute to hypoxia, and also has an immunomodulator effect; these two actions may reduce the risk of rectal bleeding and help in the management of PRD.

Evidences: According to RCT-based evidence, metronidazole is effective in treating chronic rectal bleeding and diarrhea[31,32]. Cavcić *et al*[31] randomized 60 patients with radiation-induced rectal bleeding, diarrhea and ulcerations to receive metronidazole (3 × 400 mg/d orally), mesalazine (3 × 1 g/d orally) and betamethasone enema (once a day during 4 wk) or only the combination of mesalazine and betamethasone. After 12 mo of follow-up evaluation, a significant reduction in the incidence of rectal bleeding and diarrhea was found in the metronidazole group.

Sahakitrungruang *et al*[32] enrolled in a RCT 50 patients with chronic radiation-induced PRD; patients were randomized to daily colonic irrigation plus metronidazole (3 × 500 mg/d orally) and ciprofloxacin (2 × 500 mg/d orally) for a week, or to receive 4% formalin by using proctoscopy. Outcomes were evaluated after 8 wk, showing a significant improvement in rectal bleeding, urgency, diarrhea in patients treated with metronidazole.

At the present day, these two studies represent the only RCTs showing the efficacy of metronidazole in the management of pelvic radiation disease. Other studies are recommended in order to confirm the results already achieved.

Based on the existing RCT-based evidence, metronidazole can be administered orally (3 × 400 mg/d) from 1 wk up to 12 wk. Metronidazole can be considered as a safe drug. Skin rash, nausea and vomiting are the most frequently reported side effects[32].

Probiotics

Rationale: Probiotics are defined as living microorganisms that confer a health benefit to the host when administered in adequate amounts[33]. They mainly include lactobacilli and bifidobacteria strains. The possible mechanism of action has been investigated

in various studies. Probiotics seems to have a strong immunomodulation effect by acting on epithelial cells, dendritic cells, monocytes/macrophages and lymphocytes. They also have antimicrobial activity against pathogenic bacterial strains, which is mediated by the reduction of pH, secretion of antimicrobial peptides, inhibition of bacterial invasion and adhesion to the gut epithelium[34]. They enhance barrier integrity and function, also by improving the production of short chain fatty acids, in particular butyrate[35].

In conclusion, probiotics have the potential to maintain or restore the gut microflora during and after radiation therapy, especially reducing the incidence of radiation-induced diarrhea[36].

Evidences: Up to now only one RCT has been performed and showed that probiotics are effective in treating acute diarrhea[37]. More in details, Urbancsek *et al*[37] performed a randomized, placebo-controlled, double-blind trial recruiting 205 patients with diarrhea lasting for at least 2 wk and developed within 4 wk from radiotherapy for pelvic cancers. The efficacy was inferred through the need of rescue medication per patient. After a 1 wk period of treatment, the active group required antidiarrheal drugs less frequently than placebo group, although the difference was not statistically significant. Number of bowel movements, diarrhea grading and stool consistency were also evaluated as secondary end-points, and the active group showed a significant improvement in patients' diarrhea rating and in stool consistency.

According to Urbancsek *et al*[37] *Lactobacillus rhamnosus* can be administered orally as 1.5 g sachets, three time a day, for at least one week. Probiotics, regarded as drugs or only food supplementation, can be considered as safe. No serious adverse drug reactions were reported[37].

Aminosalicylates

Rationale: Aminosalicylates are compounds that contain 5-aminosalicylic acid (5ASA), which is a potent inhibitor of the synthesis and release of proinflammatory mediators (*e.g.*, nitric oxide, leukotrienes, thromboxanes, and platelet activating factor) and also inhibits the function of several cells implicated in the acute inflammatory and immune response (*e.g.*, natural killer cells, mast cells, neutrophils, mucosal lymphocytes, and macrophages)[38]. Aminosalicylates are currently available as pro-drugs (sulfasalazine) and active compound (mesalazine). As eicosanoid inflammatory mediators are the main mediators in the pathophysiology of acute, early-onset PRD[39], the administration of aminosalicylates might be effective in reducing inflammation and therefore improve radiation-induced symptoms.

Evidences: Current evidence on the role of mesalazine in the treatment of PRD is scanty. Indeed, only one randomized, controlled trial has been performed so far, showing that mesalazine significantly improved symptoms such as diarrhea, abdominal pain and flatulence[40]. However, radiotherapy techniques have completely changed since the 70 s, thus the results of the above mentioned trial might not be suitable to present day. One prospective study assessed the efficacy of combined oral and topical mesalazine in 23 patients with chronic PRD, and found that mesalazine significantly improved rectal bleeding, but not other radiation-related symptoms (*i.e.*, pain, tenesmus and stool frequency) after 4 wk of treatment[41].

Current evidence does not support mesalazine routine use for the treatment of acute nor chronic PRD. However, a 4 wk treatment of mesalazine, once daily as a 1 g rectal suspension, might be considered in patients referred for chronic rectal bleeding developed after radiation treatment, as second-line therapy[41].

Corticosteroids

Rationale: Corticosteroids have many metabolic and physiological effects. In fact, they wield anti-inflammatory action by inhibiting the arachidonic acid cascade, blocking cytochine release and production, inhibiting histamine release and activation of macrophages and finally by stabilizing cell membranes[42]. Since the first phase of PRD development is an inflammatory based process, all the effects of corticosteroids might play a role in the early phases.

Evidences: As far as RCT-based evidence is considered, corticosteroids have not clearly shown to induce substantial benefits for treating pelvic radiation disease[31,42,43]. Cavcić *et al*[31] found that the addiction of oral metronidazole to mesalazine and betamethasone enema significantly improved rectal bleeding and diarrhea, therefore suggesting that metronidazole may have synergistic effects with steroids.

Kochhar *et al*[26] performed a double-blind controlled trial comparing sulfasalazine (500 mg three times a day) plus prednisolone (20 mg) enemas *vs* sucralfate enemas (2 g twice a day) plus oral placebo. Thirty-seven patients were enrolled and the treatment was continued for 4 wk. After the follow-up period, the sucralfate group showed a significantly better response as assessed clinically (94% *vs* 53%), thus the authors concluded that both treatment regimens were effective in the management of radiation proctopathy, though sucralfate enemas were better tolerated and had a better clinical response[26]. However, this study had a small sample size, with a follow-up period of 4 wk only, therefore detracting from any relevant conclusion.

Rougier *et al*[42] compared two different corticosteroid enemas, randomizing patients to receive either betamethasone enema (5 mg twice a day) or hydrocortisone acetate foam (90 mg twice a day). At the end of the treatment period, there was a non-significant reduction of rectal bleeding (38% *vs* 21%) in

Table 2 Endoscopic approaches for treating pelvic radiation disease

Endoscopic approaches	Rectal bleeding	Notes
Argon plasma coagulation	Y	Treatment of choice when clinically significant rectal bleeding occurs
Formalin	Y	Alternative to APC, but more prone to complications and requires more skilled endoscopist
Radio frequency ablation	N	No RCT available; possibly effective but more expensive than other treatments
Cryoablation	N	No RCT available; risk of cecal perforation
Rectal band ligation	N	Anecdotic case report

Y: Evidence supports treatment; N: Evidence does not support treatment; RCT: Randomized controlled trial; APC: Argon plasma coagulation.

favour of hydrocortisone, and betamethasone enemas were poorly tolerated in 10 of 14 patients compared with 2 of 16 patients in the hydrocortisone group. However, no firm conclusion can be drawn from this study, as patients in the betamethasone group suffered from a more severe disease and the follow-up period was too short.

Hyperbaric oxygen

Rationale: As the pathogenesis of chronic, late-onset pelvic radiation disease is mainly mediated by mucosal ischemia due to vascular sclerosis and fibrosis, and by oxidative stress, hyperbaric oxygen (HBO) therapy has been proposed. Indeed, HBO acts by inducing regrowth of injured vascular endothelial cells and epithelial cells, both directly and through stimulation of connective tissue elements[43]. HBO also improves the activity of radioprotective antioxidant enzymes and reduces free-radical damage[44,45].

Evidences: A systematic review of several case-series concluded that HBO therapy improved symptoms of radiation-induced GI toxicity in nearly 60% of patients and induced symptoms remission in 35% of patients[46]. So far, only one randomized controlled trial has been performed, comparing HBO therapy at 2.0 absolute atmospheres to normal air at 1.1 absolute atmospheres in 120 patients with chronic rectal bleeding refractory to medical treatment[47]. In this study, Clarke *et al*[47] found that HBO therapy significantly improved late-onset rectal bleeding, yielding a 32% absolute risk reduction and a number needed to treat equal to 3. However, the crossover design of the trial did not allow concluding whether symptom improvement was maintained long-term in the HBO therapy arm.

HBO should be regarded as the treatment of choice in case of chronic, radiation-induced rectal bleeding not responding to medical treatment or as second-line option in case of endoscopic failure. HBO can be considered as a relatively safe therapy, as its reported side effects were mild, transitory and self-limiting. The most frequently reported side effects are otic barotrauma, confinement anxiety and temporary myopia[47,48]. Of note, none of these side effects led patients to stop therapy[47].

ENDOSCOPIC TREATMENT

Several endoscopic techniques have been evaluated, however only argon plasma coagulation (APC) and formalin application have consistently proved to be effective for treating severe rectal bleeding. Other approaches, such as radiofrequency ablation (RFA), cryoablation and band ligation should not be considered of choice in the clinical setting (Table 2). ND: RAG laser treatment should be considered as an obsolete treatment, fully replaced by APC treatment.

Argon plasma coagulation

Rationale: Argon plasma coagulation is a noncontact technique with a governable depth of coagulation (0.5-3 mm), which applies a high-frequency current to the tissue and burns bleeding vessels, thus stopping rectal hemorrhage. As compared to ND: YAG laser therapy, APC is much more easier to use and safer; however, RCTs matching the two techniques have not been performed so far.

Evidences: The evidence supporting the employment of APC for treatment of clinically significant, intractable rectal bleeding cannot be judged as of high quality. Indeed, evidence comes from several retrospective and prospective case-series and observational studies, while only a few, small-sized RCTs comparing APC to formalin application have been conducted[49-58]. A systematic review focusing on studies published upon 2011 found that APC improved or completely resolved symptoms in 50% to 100% of patients[59]. Since then, a prospective observational study and an RCT have been published. Sato *et al*[60] performed a prospective observational study considering 65 patients with chronic rectal bleeding, and found that APC was successful in improving symptoms in 60 (94%) of them after a mean follow-up of 35 mo. Yeoh *et al*[61] randomized 30 patients with intractable rectal bleeding to receive APC or formalin endoscopic treatment, and concluded that APC was effective in treating symptoms in 94% of patients. Indeed, only one patient required further intervention after a follow-up of 111 mo.

Argon plasma coagulation should be considered as the treatment of choice when clinically significant bleeding occurs. As APC burns not only the bleeding vessels, but also mucosa and submucosa, it can lead to ulcerations, sometimes associated with chronic pain and slow healing[62]. Thus, APC should be performed reducing argon flow rates (≤ 2 L/min) and wattage (≤ 40 watt). Adverse events are mild in most cases, and have been

reported in up to 18% of patients[55]. Abdominal cramps are the most frequently described side effects, occurring due to the colonic distention induced by argon gas; thus, two-channel endoscopes should be employed in order to insufflate and contextually remove argon gas during the procedure. Ulcerations have been often reported too[62]. Severe complications have been rarely described, including gas explosion and perforation, fistula, stricture, and long-term pain[51,58,62]. Notably, colonic explosion mostly occurred when the endoscopic procedure was performed after inaccurate, local bowel cleansing with enemas, instead of gold-standard oral preparation[53,57].

Formalin

Rationale: Formalin is an aldehyde commonly used to preserve or fix tissues by cross-linkage of primary amino groups in proteins with other nearby nitrogen atoms in proteins or DNA through a CH2-linkage. As formalin is highly irritant to biologic tissues, when directly applied to radiation-damaged tissues it induces local chemical cauterization that scleroses and seals fragile neo-vasculature[63]. Thus, formalin has been proposed as a treatment for refractory severe rectal bleeding.

Evidences: Formalin might be considered as alternative to thermal coagulation therapy with argon plasma in patients with severe rectal bleeding. However, the existing evidence upon the role of formalin in PRD is not completely satisfactory: Indeed, three randomized controlled trials have been conducted so far, two of which are published in abstract form only[50,54,61]. Yeoh *et al*[61] randomized 30 patients suffering from severe rectal bleeding to receive either argon plasma coagulation or formalin application, and found that both treatments were not differently effective, as control of rectal bleeding was achieved in all patients.

Topical formalin therapy can be performed with an operating sigmoidoscope under general anesthesia. It is important to smear the anus and buttocks with petroleum jelly, in order to prevent direct contact with the formalin solution. Standard gauze pledgets soaked in 4% formalin solution have to be applied to the affected areas under direct vision, starting proximally. Each pledget needs to be held in place for 1 min for each affected area until all areas distally had been treated[61,64]. Endoscopic application of formalin is more frequently associated with complications and requires more skilled endoscopists than argon plasma coagulation therapy[65]. The most frequently reported adverse events include ano-rectal pain, fecal incontinence, severe diarrhea, fever and the severe formalin-induced colitis[66]. Other complications include anal or rectal strictures, rectal perforation or ulceration.

RFA

Rationale: RFA is an endoscopic procedure in which a target tissue is ablated using the heat generated from high frequency alternating current[67]. RFA, performed with the BARRx Halo90 system used to treat Barrett's esophagus, has been recently proposed for severe intractable rectal bleeding. In comparison with APC, RFA allows broader areas of tissues to be treated and inducess prompt squamous re-epithelialization with prevention of re-bleeding; furthermore, RFA is restricted to the superficial mucosa, thus it could represent a safer alternative to traditional endoscopic treatments[63].

Evidences: Up to now, the role of RFA as an alternative endoscopic treatment for severe intractable rectal bleeding has yet to be defined. Indeed, no randomized controlled trial has been performed, thus the quality of evidence supporting the use of RFA is poor[68-72]. Rustagi *et al*[72] performed the largest observational study concerning RFA technique in PRD. Thirty-nine patients were enclosed, and all of them experienced complete resolution of rectal bleeding during a mean follow-up of 28 mo. Furthermore, treatment with RFA led to discontinuation of blood transfusion and iron therapy in 92% and 82% of patients, respectively. As far as the existing, unsatisfactory evidence is concerned, RFA can be regarded as a relatively safe procedure[68-72]. Indeed, the most frequently reported side effects were mild-to-moderate anorectal pain, transient fecal incontinence, asymptomatic perianal ulceration and difficult evacuation of stool[70,72].

Cryoablation

Rationale: Cryoablation is a non-contact therapy that employs liquid nitrogen to apply extremely cold temperatures to a targeted area, resulting in tissue destruction. Effects are both immediate and delayed, due to the induction of ischemic necrosis.

Evidences: Up to now, the evidence supporting cryoablation as a therapeutic option for PRD is absolutely scanty. Indeed, only a few small-sized case-series have been reported[73-75]. Thus, cryoablation might not be considered as a feasible alternative to other established endoscopic treatments. The largest case series was enrolled by Hou *et al*[75] who treated with cryoablation ten patients with chronic hemorrhagic PRD and found it to significantly improve rectal bleeding. However, this was a non-powered case series pilot study, therefore these results, though attractive, are not sufficient to draw any firm conclusion. As cryoablation has not yet been performed in an adequately large sample of patient, it cannot be still considered as a safe procedure. In fact, the major risk associated with the procedure consists of colonic over-insufflation resulting in cecal perforation[75].

Rectal band ligation

A case report described the use of rectal band ligation in a patient with radiation-induced rectal bleeding not responsive to endoscopic conventional treatment, *i.e.*,

APC. Five bands were placed in two separate sessions, with nearly total eradication of rectal teleangiectasias and without complications[76]. Obviously, though encouraging this result is anecdotic, thus further studies are warranted to define the role of rectal band ligation for treating PRD.

CONCLUSION

The management of pelvic radiation disease may be challenging; several treatment options exist and the choice should be based on the best available evidences. Most of the studies have investigated the management of radiation-induced rectal bleeding. Patients with clinically significant bleeding (*i.e.*, causing chronic anemia) should firstly be considered for medical management (*i.e.*, sucralfate enemas, metronidazole and HBO), in case of failure, endoscopic treatment should be implemented. This latter should be considered the first choice in case of acute, transfusion requiring, bleeding. Alternative treatments, such as embolisation or surgery, should be considered in case of acute severe bleeding once endoscopy has failed. More well performed, high quality studies should be performed, especially the role of medical treatments should be better investigated as well as the comparative studies between endoscopic and HBO treatments.

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