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Management of Radiation-Induced Rectal Bleeding

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Abstract Pelvic radiation disease is one of the major complication after radiotherapy for pelvic cancers. The most commonly reported symptom is rectal bleeding which affects patients' quality of life. Therapeutic strategies for rectal bleeding are generally ignored and include medical, endoscopic, and hyperbaric oxygen treatments. Most cases of radiation-induced bleeding are mild and self-limiting, and treatment is normally not indicated. In cases of clinically significant bleeding (i.e. anaemia), medical therapies, including stool softeners, sucralfate enemas, and metronidazole, should be considered as first-line treatment options. In cases of failure, endoscopic therapy, mainly represented by argon plasma coagulation and hyperbaric oxygen treatments, are valid and complementary second-line treatment strategies. Although current treatment options are not always supported by high-quality studies, patients should be reassured that treatment options exist and success is achieved in most cases if the patient is referred to a dedicated centre.

Keywords Bleeding · Pelvic radiation disease · Endoscopy · Hyperbaric oxygen treatment

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Abbreviations

3D-CRT	3-dimensional conformal technique
IMRT	Intensity-modulated radiation technique
VEGF	Vascular endothelial growth factor
HIF-1α	Hypoxia-inducible factor 1α
BDP	Beclomethasone dipropionate
HBO	Hyperbaric oxygen
APC	Argon plasma coagulation
RFA	Radiofrequency ablation

Introduction

Pelvic cancers represent the most commonly diagnosed cancers and radiation therapy is one of the established treatment modalities. Prostate and uterine corpus cancers are among the 3 most common cancers among survivors [1]. Over the past 25 years, the 5-year relative survival rate for all stages combined of patients with prostate cancer has increased from 68.3 to 99.9 % and the 15-year relative survival rate is over 91 % [1]. Similarly, the 5- and 10-year relative survival rates for cancer of the uterine corpus are 81.8 and 79.5 %, respectively [1].

Radiation-induced gastrointestinal side effects can develop even after several decades; therefore, the improvement of patient life expectancy will unavoidably increase the risk of developing radiation-induced complications. Different radiation techniques are associated with different risks of complications. Patients undergoing radiotherapy with the 3-dimensional conformal technique (3D-CRT) have an increased risk of developing late-onset (>3 months) gastrointestinal toxicity in comparison to patients irradiated with the most recent intensity-modulated radiation technique (IMRT). IMRT allows the delivery of higher doses of radiation to the tumour mass while sparing the surrounding normal tissue;

conversely, larger volumes of normal tissue receive low doses of radiation compared to conventional therapies, thus reducing but not abolishing the incidence of toxicities (Table 1) [2–6]. Radiation toxicity is defined as acute when it occurs during radiotherapy or within 3 months after irradiation, while it is defined as chronic or late onset when it develops after longer time periods. The most frequent radiation-related side effects are rectal bleeding, diarrhea, urgency, and fecal incontinence, reported in about 5–50 % of patients [7–10].

Rectal bleeding is one of the most frequent manifestation of late radiation-induced side effects [11], since it is reported in up to 30–50 % of patients [7–9] and substantially influences the patient's quality of life [12, 13]. Indeed, the presence of rectal bleeding is usually associated with an increase of anxiety, anger and depression [13]. However, in most cases, bleeding is self limiting and tend to progressively disappear within weeks to months [14]. Only a minority of patients develop anaemia, and red blood transfusions are required in about 1–5 % of cases [15, 16].

In the current review, we will discuss the latest findings on pelvic radiation disease, with special interest in rectal bleeding and its management.

Pathogenesis

The pathogenesis of pelvic radiation disease is complex and involves changes in most compartments of the colo-rectal wall. During a course of radiation therapy, cellular and molecular responses will be altered, and the normal tissue that is irradiated toward the end of the treatment course differs substantially from the normal tissue that was irradiated at the beginning. In the acute phase, mucosal injuries become manifest within days after radiation exposure, and is primarily a result of cell death in the crypt epithelium, breakdown of the mucosal barriers and mucosal inflammation, thus altering the mucosal permeability. When the mucosal barrier becomes disrupted, as after radiation exposure, bacterial products and other activating agents gain access to sub-epithelial intestinal tissue where they stimulate a variety of immune cells to produce cytokines and other pro-inflammatory and anti-inflammatory mediators (i.e., IL-1, IL-6, IL-8, IL-12, IL-18, TNF-alfa) [17, 18]. In the chronic phase, the prominent structural changes include atrophy of the mucosa, fibrosis of the intestinal wall, and vascular sclerosis. Radiation-induced endothelial dysfunction leads to loss of thrombo-resistance, resulting in thrombin formation, neutrophil recruitment and activation, and stimulation of mesenchymal cells [17–20]. Thus, the typical chronic aspects are represented by connective tissue fibrosis, obliterative endoarterites and consequent neo-angiogenesis with predominant telangiectasias. Several mediators have been implicated in the pathogenesis of radiation-induced angiogenesis, such as vascular endothelial growth factor (VEGF) [21] and hypoxia-inducible factor 1α (HIF-1α) [22]. Therefore, the development of rectal bleeding is strictly related to this neo-angiogenic process, since these superficial neo-vessels are immature and particularly fragile and the stool passage is sufficiently traumatic to induce bleeding. Furthermore, it should be pointed out, from a clinical point of view, that most of the varied manifestations of late-onset injury are unrelated to active inflammation.

Table 1 Incidence of radiation-induced rectal bleeding according to tumour site and radiotherapy technique

Tumor site	Radiotherapy technique	Toxicity score system	Follow-up (months)	Rectal bleeding incidence
Anal canal	3D-CRT	NCI-CTCAE	24	Grade ≥3, 3 %
	IMRT	NCI-CTCAE	24	Grade ≥3, 7 %
Prostate	3D-CRT	RTOG	12	Grade ≥2, 11 %
	IMRT	RTOG	12	Grade ≥2, 7 %
Cervix	3D-CRT	RTOG	36	Grade ≥2, 30 %
	IMRT	RTOG	36	Grade ≥2, 12 %

Prevention

Once developed, the management of pelvic radiation disease may be challenging. Therefore, many efforts have been conducted in order to prevent the trigger mechanisms behind the development of radiation-induced damages. The administration of cytoprotective and anti-inflammatory drugs during the radiation treatment has been advocated as a possible preventive strategy and been widely investigated. The rationale is to reduce the damage to normal tissues surrounding the irradiated fields by reducing or abolishing the inflammatory process (i.e., beclomethasone dipropionate, mesalazine) [13, 23, 24], by constituting a mechanical shielding against aggressive luminal factors (i.e. sucralfate) 25, 26], by preventing with free radical scavengers the radiation-induced direct DNA damage (i.e. amifostine) [27, 28], by reducing pancreatic secretion and intestinal motility (octreotide) [29], and by acting on the intestinal bacterial flora (i.e. probiotics) [30].

However, as previously reported, the pathogenesis of pelvic radiation disease is complex and not yet fully understood, and therefore only a few agents have been reported to have clinically significant preventive effects and usually for only 1 symptom (i.e. bleeding or diarrhoea).

In 2011, we reported our experience with a non-systemic glucorticosteroid, beclomethasone dipropionate (BDP) [13]. We investigated in a double-blind, placebo-controlled randomised trial, whether topical rectal beclomethasone dipropionate treatment can prevent the development of pelvic radiation disease in patients who underwent radiotherapy

for prostate cancer. Patients were treated with a 3-mg BDP enema or identical-looking placebo the evening before each radiation session, for the entire duration of radiotherapy. Immediately after the end of radiotherapy, patients stopped the enema formulation and received two 3-mg beclomethasone dipropionate suppositories, or identical placebo, for 4 more weeks. Between June 2007 and October 2008, 120 patients were randomized, 60 patients in the BDP arm and 60 patients in the placebo arm. After 12 months of follow-up, patients treated with BDP presented a significant reduction of the post-radiation risk of bleeding (OR 0.38; 95 % CI 0.17–0.86) and of rectal mucosal changes. In particular, actively treated patients presented fewer rectal angiectasias in comparison to non-treated patients. Most importantly, at the end of follow-up, patients on BDP presented a higher Quality of Life score, in particular BDP preventive treatment seemed to better preserve the patient's emotional status (e.g., anger, depression, irritability), which was less frequently altered.

Based on the results of our randomised controlled trial, we suggested considering a preventive strategy based on beclomethasone dipropionate in patients with pelvic cancer and scheduled for radiation treatment. Furthermore, BDP-based treatments should be especially considered for patients at increased risk of developing radiation-induced side effects. Several patient-related risk factors have been identified [31]. Since endothelial dysfunction, inflammation, and connective tissue alterations have an important role in the pathogenesis of pelvic radiation disease, patients with diabetes, inflammatory bowel diseases (i.e., Crohn's disease, ulcerative colitis), and collagen vascular disease (scleroderma, systemic lupus erythematosus) have an increased risk of developing severe acute and late toxicities. Patients with these clinical conditions might have the maximum beneficial effect from a preventive treatment.

Therapy

The management of radiation-induced rectal bleeding can be challenging. A step-by-step approach, including medical, endoscopic, and hyperbaric oxygen treatments is advisable. It should, however, be pointed out that most of the mild cases of bleeding, generally represented by patients reporting traces of blood during or at the end of the evacuation process, tend to solve spontaneously within weeks to months. Therefore, treatments should be focused only on those patients presenting with a clinically significant bleeding (i.e. needing transfusion), with a documented drop of the haemoglobin level or with a significant impact on quality of life, despite the reassurance provided by the physicians.

All patients reporting rectal bleeding must be investigated with flexible sigmoidoscopy or, alternatively, with full colonoscopy in cases of patients with unexplained anaemia after sigmoidoscopy, with anaemia refractory to treatments and with a personal or family history of colorectal cancer.

Medical Therapy

Medical therapy should represent the first step in the management of radiation-induced rectal bleeding. In the last decades, several medical therapies have been examined. These have mostly been treatments that are useful for idiopathic inflammatory bowel disease (5-aminosalicylates, corticosteroids, sucralfate, metronidazole and short-chain fatty acids). However, a systematic review of both randomised and non-randomised, prospective and comparative trials showed that steroids and 5-aminosalicylic acids, which are often erroneously suggested as first-line treatment for pelvic radiation disease, have no beneficial effects [32, 33••].

At the moment, just a few treatments have shown, in randomised controlled trials, to be effective for the treatment of radiation-induced rectal bleeding: metronidazole [34] and sucralfate enemas [35].

The rationale of antibiotic therapy in the treatment of radiation-induced bleeding has not been deeply investigated. It has been supposed that metronidazole acts on microorganisms, such as anaerobic and microaerophilic bacteria, that contribute to hypoxia, and this selective toxicity of metronidazole, together with an immunomodulator effect, may reduce the risk of bleeding. Cavcic and co-workers [34] randomised 60 patients with radiation-induced rectal bleeding and diarrhea to metronidazole (3×400 mg orally per day) plus mesalazine and betamethasone or to mesalazine and betamethasone, but without metronidazole, and found, after 12 months of follow-up, a significant reduction in the incidence of rectal bleeding and ulcers as well as a significant decrease in diarrhea in the metronidazole group.

The mechanism of action of sucralfate is thought to be stimulation of epithelial healing and the formation of a protective barrier overlying damaged mucosal surfaces; indeed, sucralfate is a sucrose sulphate-aluminium that stimulates epithelial healing. Kochhar and co-workers [35], based on a randomised study including 37 patients with pelvic radiation disease, found a significantly better clinical response in patients treated with sucralfate enemas (2 g sucralfate twice a day) compared to control. Eight of nine patients (89 %) receiving sucralfate enemas improved versus three of five (60 %) patients receiving hydrocortisone [OR 1.48, 95 % CI (0.70–3.14)]. Furthermore, based on the effect of sucralfate on epithelial healing, sucralfate enemas are particularly indicated for the treatment of rectal ulcers. Sucralfate enemas should be composed in the following manner: 2 g sucralfate suspension made-up with 30–50 mL water in a bladder syringe injected

twice a day via a lubricated foley catheter passed through the anus into the rectum.

Similarly, butyrate and short-chain fatty acids exert a trophic effect on the rectal and colonic mucosa and stimulate mucosal blood flow. Small, randomised trials have showed a beneficial effect of topical rectal treatment with butyrate and short chain fatty acids only for acute onset radiation-induced bleeding but not for chronic, late-onset symptoms [36–38].

Endoscopic Therapy

Once medical therapies have failed, two alternative treatments may be proposed. In cases of chronic rectal bleeding associated with a slow decline of the haemoglobin level, hyperbaric oxygen (HBO) therapy should be taken into account. Otherwise, in cases of acute, clinically significant, bleeding or unavailability of HBO therapy, endoscopic treatments should immediately be suggested.

The goal of endoscopic therapy is to achieve control of bleeding and to improve the quality of life, reducing the need of blood transfusions and hospital admissions. Endoscopic therapy uses several modalities such as thermal therapy and formalin therapy and, more recently, radio-frequency ablation and cryoablation. The two techniques most frequently used are the thermal coagulation therapy with argon plasma and the formalin therapy.

Argon plasma coagulation (APC) is a noncontact technique with a controllable depth of coagulation (0.5–3 mm). High-frequency current is applied to the tissue through ionised and electrically conductive gas, called argon plasma; the diverging gas flow allows an axial, radial and retrograde application. In comparison to Nd:YAG laser therapy, APC is easier to use, more manageable, cheaper and, most importantly, safer; nevertheless, randomised trials comparing the two endoscopic procedures are lacking. Thermal therapy burns bleeding vessels but also mucosa and submucosa. According to a recent systematic review, the reported success rates of APC treatment ranged from 50 to 100 % [39]. Adverse events are generally mild, reported in about 0–18 % [40]. Patients on anticoagulant or antiplatelet therapies have higher recurrence rates and require a higher number of APC sessions [41]. Abdominal cramps, due to the colonic distension from the instillation of argon gas, are the most frequently adverse event reported during and soon after the procedure; for this reason, it is recommended using two channels endoscope to insufflate argon gas and removing it from the second channel and set the argon flow rate at the lowest effective level (0.8–2 L/min) [42]. In order to reduce the risk of complications, more than one session is generally needed for the treatment of rectal teleangiectasias covering the entire rectal surface. Although a study comparing APC at 2 different power settings, 40 versus 60 W, did not find any difference between the two treatment groups [43], it is advisable to set the power at the lowest level in order to further reduce the risk of complications. Severe complications have been rarely reported, such as gas explosions, perforation, stricture, fistula or long-term pain [44–46]. Several studies and case-reports have observed that colonic explosion, with or without perforation, mostly occurred when only local preparation with enemas was performed instead of oral preparation for full bowel cleansing [47, 48]. It has been supposed that argon gas, mixed with intestinal gas and fermentable products of the enemas, could promote gas explosions. Rectal ulcers are frequently observed in follow-up endoscopy, especially when higher wattage is used and in patients with predisposing factors, such as diabetes, cigarette smoking habit, and aspirin treatment (Fig. 1).

Formalin solution (4–10 % solution) is directly applied to the tissue with a catheter and produces local chemical cauterisation that scleroses and seals fragile neo-vasculature in radiation-damaged tissues. A retrospective study, comparing APC and formalin application, showed an improvement in 11 of 14 patients (78 %) that underwent APC versus 3 of 11 patients (27 %) who received topical formalin therapy, yielding an OR of 9.7 (95 % CI 1.1–91.0) [49]. Otherwise, two small, randomised, controlled studies, published in abstract form, did not find any difference between the two methods [50, 51]. After all, it should stressed that rectal instillation of formalin solution is more prompt to complications and requires more skilled and experienced endoscopists [52]. The most frequently reported adverse events include ano-rectal pain, faecal incontinence, severe diarrhoea, fever and, finally, the severe formalin-induced colitis. This is because it can be difficult to stop formalin extending proximally outside the treatment area, particularly with the instillation technique. Other complications include anal or rectal strictures, rectal perforation or ulceration.

Radiofrequency ablation (RFA), performed with the BARRx Halo90 system, routinely used for ablating Barrett's

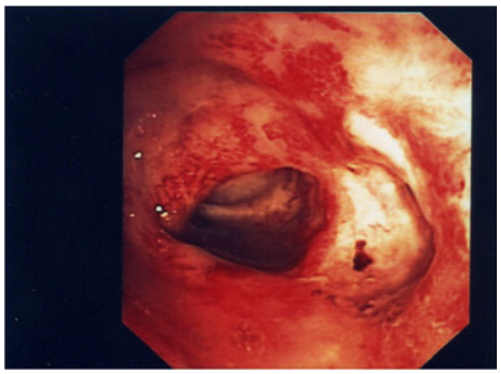

Fig. 1 Radiation-induced rectal ulcer and multiple angiectasias in a patient irradiated for prostate cancer. The ulcer developed after argon plasma coagulation treatment (2 L/min; 60 W). The patient presented several comorbidities and predisposing factors, since he was diabetic and on dual antiplatelet chronic treatment

oesophagus, has been proposed as an alternative endoscopic treatment. Potential benefits include squamous re-epithelialisation seen after RFA with prevention of re-bleeding. Furthermore, RFA allows much broader areas of tissues to be treated in comparison to the point-by-point approach required with APC. Since the ablative treatment is restricted to the superficial mucosa and deep tissue injury is avoided, this endoscopic treatment could represent a safer alternative; at the moment, only a few case-series [53, 54] have been published and results from large, prospective trials are awaited before drawing any conclusions.

Cryoablation is a non-contact therapy based on the use of liquid nitrogen. Tissue destruction is achieved by the application of extreme cold temperatures to a targeted area, and the effects are both immediate and delayed, due to the induction of ischemic necrosis. At the moment, only a few case-reports and series have been published, and bleeding resolution was reported in about 80–100 % of cases [55–57]. This technique presents several limitations. The major risk associated with the procedure is represented by the colonic over-insufflation that can induce cecal perforation [57]; therefore, a decompression tube is routinely placed in the rectum during the procedure and a full colonoscopy after treatment is advisable to further decompress the colon [57]. The commercially available cryotherapy unit is heavy and difficult to carry, and requires the maintainance of a constant supply of liquid nitrogen, which actually lasts no more than 2 weeks in the current storage tank. The long-term effects of the induction of delayed ischemic necrosis might further worsen the pelvic radiation disease, which is mainly due to an ischemic process. Since the safety profile and long-term sequelae are as yet poorly known, cryoablation should be considered only in the setting of controlled clinical trials.

Finally, a recently published case report used rectal band ligation in a patient with frequent episodes of radiation-induced proctorrhagia, refractory to APC treatments. A total of 5 bands were placed in two separate sessions, without side effects and an almost complete eradication of rectal angiectasias [58]. Further studies are needed before suggesting this approach in the current practice.

Hyperbaric Oxygen

Hyperbaric oxygen therapy represents an alternative treatment for radiation-induced gastrointestinal side effects. The ischemic process has a pivotal role in the development of late-onset, chronic complications of radiotherapy. Based on the evidence that HBO induce angiogenesis, increase the activity of radio-protective antioxidant enzymes, stimulate tissue regeneration, reduce free-radical damage, decrease tissue fibrosis, and stimulate collagen formation through the increase of local tissue oxygen tensions, it has been proposed for more than 20 years for the treatment of radiation-induced disease.

Several case-series suggested that about 60 % of patients with radiation-induced toxicity experienced a clinical improvement after hyperbaric oxygen therapy and 35 % of patients reported a complete remission [59].

At the moment, only one randomised, controlled, double-blind, crossover trial has been performed, comparing HBO at 2.0 atmospheres absolute to air at 1.1 atmospheres absolute in patients with refractory pelvic radiation disease [60••]. In this study, Clarke and co-workers randomised 120 patients and found that patients treated with hyperbaric oxygen therapy had a significant improvement with an absolute risk reduction of 32 % and a number needed to treat of 3 [60••]. Unfortunately, the crossover design did not allow the determination of whether the beneficial effects were maintained even in the long-term period.

HBO is a safe treatment, and the reported side effects are generally transient, self-limiting and mild (otic barotrauma, confinement anxiety and temporary myopia) [61]; furthermore, it may improve symptoms other than gastrointestinal toxicity (i.e. genito-urinary toxicity). Otherwise, it is not universally available, is time-consuming since it lasts 6–8 weeks and, finally, it is an expensive procedure.

HBO should be considered the treatment of choice in case of chronic, radiation-induced bleeding refractory to medical treatment or as second-line treatment in case of endoscopic failure.

Conclusions

Radiation-induced bleeding is a frequently reported adverse event, which develops after the treatment of pelvic cancer. As more patients survive cancer, there will be an increasing number of patients with late effects from radiation treatment. Bleeding is generally a self-limiting complication due to the growth of new, fragile mucosal vessels in the sigma-rectum and only a minority of cases need treatment, because of the development of anaemia. A flexible sigmoidoscopy or, in selected cases, a total colonoscopy to exclude other causes of bleeding should be immediately suggested. In the absence of clinically significant bleeding, the physician should reassure the patient and provide stool softeners. In cases of more severe bleeding, medical therapies, such as sucralfate enemas and metronidazole, should be proposed, although limited evidence is available on their efficacy. Endoscopic therapy, mainly represented by argon plasma coagulation, has proven to achieve the control of bleeding in about 80 % of cases; however, complications are not negligible and patients should be fully informed and the procedure performed in experienced and high-volume centres. Where available, hyperbaric oxygen therapy should be considered, especially in the setting of

chronic bleeding. Although current treatment options are not always supported by high-quality studies, patients should be reassured that treatment options exist and that success is achieved in most cases if the patient is referred to a dedicated centre.

Compliance with Ethics Guidelines

Conflict of Interest Liboria Laterza, Paolo Cecinato, Alessandra Guido, Alessandro Mussetto and Lorenzo Fuccio declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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