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RESPONSIBLE EDITORS FOR THIS ISSUE

Hyperbaric oxygen therapy as a complementary treatment for radiation proctitis: Useless or useful? – A literature review

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Abstract

Radiotherapy (RT) is the backbone of multimodality treatment of more than half of cancer cases. Despite new modern RT techniques, late complications may occur such as radiation proctitis (RP). The natural history of RP is unpredictable. Minor symptoms may resolve spontaneously or require conservative treatment. On the other hand, for similar and uncomplicated clinical contexts, symptoms may

persist and can even be refractory to the progressive increase in treatment measures. Over the last decades, an enormous therapeutic armamentarium has been considered in RP, including hyperbaric oxygen therapy (HBOT). Currently, the evidence regarding the impact of HBOT on RP and its benefits is conflicting. Additional prospective and randomised studies are necessary to validate HBOT's effectiveness in the 'real world' clinical practice. This article reviewed the relevant literature on pathophysiology, clinical presentation, different classifications and discuss RP management including a proposal for a therapeutic algorithm with a focus on HBOT.

Key Words: Radiation proctitis; Radiation proctopathy; Radiotherapy; Radio-induced lesion; Late radiation tissue injury; Delayed radiation injury; Late sequelae; Hyperbaric oxygen therapy; Hyperbaric oxygen; Review

Core Tip: Over the last decades, an enormous therapeutic armamentarium has been considered in radiation proctitis (RP) management including hyperbaric oxygen therapy (HBOT). However, evidence regarding the impact of HBOT on RP and its benefits is conflicting. With the lack of consensus to guide the use of HBOT for the treatment of RP, the goal of this review was to synthesise the existing data, analyse results of previous studies, identify gaps in knowledge, and discuss RP' management including a proposal of a therapeutic algorithm focusing on HBOT.

INTRODUCTION

In recent years and on a global scale, we have witnessed a sustained increase of cancer incidence, with a steady growth rate of approximately 3% per year. According to the International Agency for Research on Cancer of the World Health Organization, it is estimated that worldwide the number of new cancers will reach almost 30 million in 2040, with a mortality of 16.5 million[1].

However, these alarming numbers may be related to the implementation of screening programs with the detection of more cases of cancer at an early stage. Moreover, the survival rates of patients diagnosed with cancer have also increased, largely due to scientific development and the commitment of health professionals in oncology. The progressive increase of this new population cancer survivors with specific clinical and social problems poses a real healthcare challenge. It is in this particular context that radio-induced lesions arise, taking into account their prevention and treatment.

In developed countries, radiotherapy (RT) is the backbone of multimodality treatment of more than half of cancer cases. Despite new modern RT techniques, delayed radiation injury can appear with a latency period of a few months to several decades. The incidence and prevalence of radio-induced lesions and their severity are not well known due to different definitions, underestimation of mild symptoms by both patients and professionals, and the imprecise notification of their appearance in clinical practice[2].

RT is a key treatment of the multimodal approach of neoplasms of the gastro-intestinal and pelvic regions. The fixed anatomical position of the rectum in the pelvic brim and the proximity to the irradiated organs makes the rectum especially vulne-rable to secondary ionising radiation injury[3]. Radiation proctitis (RP) or radiation proctopathy is defined as a chronic lesion of the mucosa and submucosa of the rectum or rectosigmoid transition secondary to ionising radiation[3].

Acute radio-induced lesions occur from hours or days after exposure to ionising radiation and usually resolve in less than 3 mo. On the other hand, RP is a late lesion with a median onset of 6 to 12 mo after exposure. Rare cases with a latency over 30 years have been reported. Furthermore, RT can develop a continuous process from an acute injury, where symptoms are not specific or non-existent. The clinical presumption is based on intestinal symptoms (*e.g.*, haematochezia, diarrhoea, tenesmus, abdominal pain) and in a cause-effect relationship of previous history of pelvic RT. The diagnosis can be confirmed by endoscopy with or without histologic examination, as imaging findings are usually nonspecific[4-12].

Virtually all patients will experience some clinical manifestation of acute RP during their pelvic RT treatment[8]. Previously, it was thought that only a minority of patients (5%-15%) would develop RP[9,13,14]. However, based on recent data, it is now estimated that near half of the patients may report symptoms related to RP[14,15]. Following RT, 30% of patients with prostate cancer, 12%-17% with rectal cancer, 16% with testicular cancer and 10% with cervical cancer will develop RP[16]. RP's most severe cases have an estimated 4.3%-22% incidence and a 2%-8% mortality rate[11-16].

A high risk of developing RP depends on the total radiation dose and its fractionation, the mode of application (external *vs* intracavitary), the volume of irradiated tissue and the combination of RT techniques. A cumulative dose of RT < 45 Gy is associated with a lower risk of late RT lesion in contrast to what is observed for doses > 70 Gy, for which the risk is significantly higher. The RT technique used is an essential predictor of risk for RP. Compared to brachytherapy, ionising radiation typically administered through a linear accelerator will result in greater and more significant exposure of the contiguous organs. The new RT modalities that comprise three-dimensional conformational RT, intensity-modulated RT and proton and neutron therapies seem to be associated with a lower risk of gastrointestinal toxicity[5-9,17,18].

Advanced age, low body mass index, smoking habits, previous abdominal surgery due to intraperitoneal adhesions, pelvic inflammatory disease, arterial hypertension, diabetes mellitus, previous chemotherapy, collagen and vascular diseases, xeroderma pigmentosa, Cockayne syndrome are other patient-related factors that may be associated with a higher RP risk. Among this array of risk factors, those that seem to have the most significant predictive value for RP are the history of abdominal surgery, chemotherapy, arterial hypertension, and thinness[5-13].

Although the processes of obliterating endarteritis, hypoxia, and fibrosis are already recognised as fundamental factors for their establishment and eventual evolution to chronicity, RP's pathophysiology is complex and has not yet been fully understood[12,19-21]. This chronic condition can stabilise or gradually worsen with periods of acute inflammation.

The beneficial properties of hyperbaric oxygen, together with the growing knowledge about the pathophysiology of delayed radiation injuries, have led to the use of hyperbaric oxygen therapy (HBOT) in the treatment of RP[4]. Currently, HBOT is considered by the European Committee for Hyperbaric Medicine (ECHM) as a treatment modality for late radio-induced lesions, namely, the prevention and treatment of osteoradionecrosis of the mandible, haemorrhagic radiation cystitis and RP (degree of recommendation I/level of evidence B). Although HBOT is used in selected cases of other RT sequelae (*e.g.,* central nervous system and radio-induced laryngeal lesion), its degree and level of recommendation/evidence is lower[22].

Attending to the lack of consensus on guidelines for the use of HBOT in the treatment of RP, the goal of this review is to synthesise the existing data, analyse results of previous studies, identify gaps in knowledge, and discuss RP' management including a proposal for a therapeutic algorithm with a focus on HBOT.

RP PATHOPHYSIOLOGY

Ionising radiation can cause cellular damage, especially in mucosa with rapid renewal such as the intestinal mucosa.

Acute lesions occur predominantly in the mucosa, which consists of depletion of epithelial cells due to cytotoxicity in progenitor cells and consequent apoptosis; inflammation and infiltration of the lamina propria with polymorphonuclear leukocytes and plasma cells; eosinophilic abscesses of intestinal crypts; endothelial lesions of intestinal microvascularisation and eventual oedema of the submucosa. These processes result in mucositis that interferes with the intestinal barrier's function, allowing antigen translocation including microorganisms[23]. If the submucosa

modifications are not impactful, the epithelial cells regenerate and the process resolves spontaneously (Figure 1).

Parallel to what has been described for other late sequelae of RT, RP's pathophysiological mechanisms are not fully understood. Oxidative stress caused by reactive oxygen species (ROS) contributes to obliterating endarteritis with progressive reduction of parietal irrigation and consequent local ischaemia, formation, and diffuse progression of mucosal and submucosal fibrosis through a local proinflammatory cytokines cascade (high levels of interleukin-1β (IL-1β), IL-2, IL-6, IL-8, and transforming growth factor-β), which is promoted by macrophages, neutrophils, and by the differentiation of fibroblasts into myofibroblasts (Figures 1 and 2)[5,23-25]. Recently, an unique intestinal microbiota signature has been identified in an animal model of RP, which seems to be capable of increasing the expression of IL-1β, IL-6, and tumour necrosis factor-α (Figure 2). Mice colonised with previously irradiated intestinal microbiota were more prone to RP than the control colonised with naïve intestinal microbiota[26]. Furthermore, it is postulated that the microbiota can also influence the efficacy of the cancer treatment *per se*.

This transmural pathological regenerative process of the intestinal wall will exacerbate the progressive decrease in vascular density (and consequently the formation of friable telangiectasias and lymphatic vessels dilation), cell depletion, mucosal atrophy, and stenosis of the intestinal wall. Moreover, chronic mucosal ulcers can predispose to haemorrhage, the formation of fistulae and possible risk of intestinal perforation (Figure 2)[6,8,9].

CLINICAL PRESENTATION

Clinically, RP presents itself in two forms: acute or chronic. The acute form is typically resolved within a few weeks and it is characterised by nausea, vomiting, abdominal pain, diarrhoea, urgency, tenesmus, and more rarely, lower gastrointestinal bleeding. The chronic form has a similar clinical presentation; however, it is characterised by an indelible evolution, leading, in the most severe cases, to major digestive haemorrhage, chronic constipation, faecal incontinence, severe proctalgia, stenosis, fistulisation and eventually, intestinal perforation. Moreover, patients may also have other symptoms resulting from pelvic irradiation such as radiation enteritis, haemorrhagic radiation cystitis or urethral stricture. The occurrence of colorectal neoplasms induced by radiation has also been described, mostly after a long latency period, which can be manifested by masses or non-healing ulcers[5,7,8].

For diagnosis, a cause-effect relationship should be established between the history of pelvic RT and intestinal symptoms. A rectal examination will evaluate anal sphincter tonicity and a rectosigmoidoscopy the mucosa characteristics and affected areas, excluding malignancy. Total colonoscopy can be considered to outline the true extent of the disease and/or exclude the possibility of another aetiology for colitis. Endoscopic images usually reveal a pale, friable mucosa, with telangiectasias and/or ulcerations, and a clear separation between the altered and normal region, corresponding to the irradiated zone's limit. A biopsy is usually not recommended to confirm the diagnosis because it may increase the risk of complications[7,8].

In addition, it is essential to exclude other possible causes of subacute or chronic proctitis such as inflammatory bowel disease, diverticular colitis, atherosclerotic disease or previous episodes of chronic ischemic colitis, chronic exposure to the effects of non-steroidal anti-inflammatory drugs, recent use of antibiotics that predispose to *Clostridioides difficile* infection, parasitic (*e.g.*, amebiasis) or bacterial (*e.g.*, *Salmonella* spp., *Campylobacter* spp.) infections due to recent travelling to endemic countries, history or risk factors for sexually transmitted diseases (*e.g.*, *Neisseria gonorrhoeae* and herpes simplex virus) and cytomegalovirus infection in the immunocompromised patient[7,8].

In several studies, the severity of RP is objectively graded using symptom scores, such as the Radiation Proctopathy System Assessment Scale or the Late Effects Normal Tissue (LENT-SOMA) scale and considering the intraluminal findings by endoscopic grade (modified Chi grading or scales Chutkan and Gilinski). The comparison of data between studies is difficult due to the use of different severity scores. The same is true for outcome measures. Table 1 summarises some of the different classifications of RP that have been proposed in the literature[27-37].

Table 1 Classification of stages/grades of radiation proctitis

Ref.	Stages/grades	Description
Sherman[27], 1954	I-IV	Based on endoscopic findings: I: (a) Localised erythema and telangiectasia, friable mucosa with easy bleeding: no ulceration or stricture formation, and (b) More diffuse erythema along with periproctitis, marked pain, and sensitivity; II: Presence of ulceration with a greyish tenacious slough, usually involving the anterior rectal wall, and proctitis with grade I lesions; III: Presence of rectovaginal fistulae or bowel perforation and varying degrees of proctitis with ulceration; IV: Presence of rectovaginal fistulae or bowel perforation and varying degrees of proctitis with ulceration.
Dean and Taylor[28], 1960	I-III	Based on clinical and endoscopic findings: I: Symptoms: Rectal bleeding, tenesmus, sphincter instability, mucoid discharge; endoscopic findings of vascular congestion, friability of the mucosa, mucosal thickening, mucoid discharge; II: Same symptoms as before; endoscopic findings of ulcerations, underlying thrombosis of the small vessels; III: Same symptoms as before plus perineal sepsis, incontinence, diarrhoea, perianal purulent discharge; endoscopic findings of necrosis, fistulae, strictures.
Gilinsky *et al*[29], 1983	Normal; Mild; Moderate; Severe	Based on endoscopic findings: Score 0: Normal mucosa; Score 3: Erythema and/or telangiectasia, oedema, thickening, pallor of mucosa; Score 6: Friability; Score 9: Ulceration and/or necrosis.
Langberg *et al*[30], 1992	1-3	Based on histopathologic findings: Thickening of serosa: (1) Slight thickening of serosa, hyperplasia of peritoneal mesothelium; and (2) Marked thickening of serosa; and (3) Extreme thickening and fibrosis serosa. Mucosal alterations: (1) Small superficial ulcerations; and (2) Ulcerations involving more than half of the intestinal circumference. Epithelial atypia: (1) Abnormally oriented crypts; (2) Irregular crypt regeneration with atypical epithelial cells; and (3) Adenocarcinoma. Vascular sclerosis: (1) Slight double normal thickness, broadened and hyalinised collagen fibres; (2) Submucosa three to four times normal thickness, abnormal collagen fibres; and (3) Massive fibrosis including muscularis. Lymph congestion: (1) Dilated lymph vessels or cystic collections of lymph. Ileitis cystica profunda: (1) Submucosal glandular inclusions; (2) Submucosal cysts with polypoid elevation of the mucosa; and (3) Large cysts extending into the muscularis.
Chutkan *et al*[31], 1997	0-4	Based on clinical findings: 0: No haemorrhage; 1: Blood on toilet paper or mixed with faeces; 2: Drops of blood in the toilet; 3: Severe haemorrhage with expulsion of clots; 4: Haemorrhage that requires transfusion.
Wachter *et al*[32], 2000. Vienna Rectoscopy Score	0-5	Based on endoscopic findings: Score 0: Congested mucosa (grade 1); Score 1: Congested mucosa (grade 2), telangiectasia (grade 1); Score 2: Congested mucosa (grade 3), telangiectasia (grade 2); Score 3: Congested mucosa (any grade), telangiectasia (grade 3), ulceration (grade 1); Score 4: Congested mucosa (any grade), telangiectasia (any grade), ulceration (grade 2), stricture (grade 1); Score 5: Congested mucosa (any grade), telangiectasia (any grade), ulceration (grade 3), stricture (grade 2), necrosis (any grade).
Zinicola *et al*[33], 2003. Bleeding Scale for Radiation-Induced Haemorrhagic Proctitis	0-4	Based on clinical findings: 0: No bleeding; 1: Intermittent bleeding (once weekly or less); 2: Persistent bleeding (twice or more weekly); 3: Daily bleeding or anaemia; 4: Require blood transfusion.
Chi *et al*[34], 2005. RTD grading scale	0-3	Based on RTD endoscopic findings: 0: Normal mucosa; 1: < 10 telangiectasias; 2: > 10 telangiectasias; 3: Confluent lesions, active bleeding or friable mucosa.
Ehrenpreis *et al*[35], 2005. Radiation Proctopathy System Assessment Scale (RPSAS)	1-5	Based on clinical findings: Diarrhoea. Urgency. Rectal pain. Tenesmus. Rectal bleeding. Faecal incontinence. Severity: 1: No problem. 2: Mild problem–can be ignored when you do not think about it. 3: Moderate problem–cannot be ignored; no effect on ADL. 4: Severe problem–influences your concentration on ADL. 5: Very severe problem–markedly influences your ADL and/or requires rest. Frequency: 1: Monthly; 2: Weekly; 3: Several times *per* week; 4: Daily; 5: Throughout the day.
Cox *et al*[36], 1995. Late Radiation Morbidity Scoring Criteria Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer	0-5. Late (> 3 mo)	Based on clinical and imaging findings: 0: No changes; 1: Mild diarrhoea, mild cramping, bowel movement 5 times daily, slight rectal discharge or bleeding; 2: Moderate diarrhoea or colic, bowel movement > 5 times daily, excessive rectal mucus or intermittent bleeding; 3: Obstruction or bleeding requiring surgery; 4: Necrosis, perforation, or fistulae; 5: Death related to adverse event.
NCI CTCAE version 5.0[37], 2017	1-5	Based on clinical findings: 1: Mild adverse event; rectal discomfort, intervention not indicated; 2: Moderate adverse event; rectal discomfort, passing blood or mucus, medical intervention indicated, limiting instrumental ADL; 3: Severe and undesirable adverse event, faecal urgency or stool incontinence, limiting self-care ADL; 4: Life-threatening or disabling adverse event, urgent intervention needed; 5: Death related to adverse event.

ADL: Activities of daily living; RTD: Rectal telangiectasia density.

RP TREATMENT

The treatment of acute RP is essentially symptomatic and in accordance with the guidelines for the treatment of mucositis of other aetiologies[38,39]. In the absence of response to first-line antidiarrheal medication, it must be recommended treatment with octreotide or other somatostatin analogues and butyrate enemas that seem to accelerate the intestinal mucosa regeneration process. There is clinical evidence that
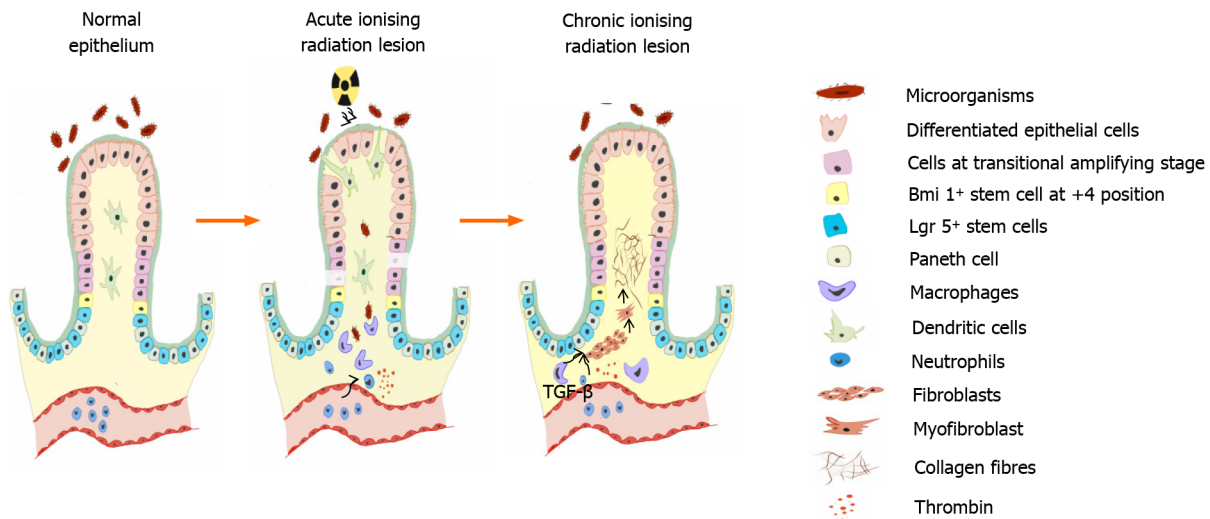
Figure 1 Representative scheme of intestinal injury induced by ionising radiation. In a healthy gut, crypts are with intact mucosa. Lgr5+ stem cells proliferate and cells migrate upwards to provide differentiated epithelial cells of the villi. Acute lesions occur predominantly through different pathological processes: Depletion of epithelial cells due to cytotoxicity in progenitor cells and consequent apoptosis; inflammation and infiltration of the lamina propria with polymorphonuclear leukocytes and plasma cells; eosinophilic abscesses of intestinal crypts; endothelial lesions of intestinal microvascularisation with the release of thrombin and eventual oedema of the submucosa; influx of antigenic material, including gut microbiota into the lamina propria. If the submucosa modifications are not impactful, the epithelial cells regenerate, and the process resolves spontaneously. The constitutive and chronic phase comprises obliterating endarteritis with progressive reduction of parietal irrigation and consequent local ischaemia; formation and diffuse progression of mucosal and submucosal fibrosis through a local proinflammatory cytokine cascade (high levels of interleukin-1β (IL-1β), IL-2, IL-6, IL-8, and transforming growth factor-β), which is promoted by macrophages, neutrophils and by the differentiation of fibroblasts into myofibroblasts. Citation: Adapted from Costa *et al*[21] and Kumagai *et al*[23].

intrarectal amifostine (ROS scavenger) could be, in selected patients, a possible protective pharmacological measure against the acute effects of RT. Generally, the acute RP is a self-limiting situation, although in about 20% of cases, it is necessary to suspend or even interrupt RT treatments[7,38,39].

The natural history of RP *per se* is unpredictable. Minor symptoms may resolve spontaneously or require conservative treatment. On the other hand, symptoms may persist for similar and uncomplicated clinical contexts and become refractory to the progressive increase in therapeutic intervention. Thus, early diagnosis and intervention are essential and symptoms should not be overlooked, even if they have little impact on the patient's quality of life (QoL).

The management of RP can be challenging and requires a holistic approach for which there is no gold standard protocol. Furthermore, there are no prophylactic measures that have been shown to be beneficial in reducing RP incidence. Concerning treatment options, most of the clinical evidence is based on case studies and small series. Therapeutic management should be personalised according to the patient, the severity of the clinical condition, and the institution's experience. The non-invasive or minimally invasive measures include changing the diet and symptom control with pharmacological and endoscopic support. In terms of medical treatment, the intrarectal application of formalin (4%-10% formaldehyde) and sucralfate enemas stand out as effective measures to control bleeding in patients with haemorrhagic RP. Studies present conflicting results for the use of short-chain fatty acid enemas. There is a lack of scientific evidence to recommend the use of alternative treatments such as mesalamine, ozone therapy, metronidazole, vitamin A, antioxidant vitamin complexes (vitamin C and E) and pentoxifylline. Endoscopic treatment with plasma argon has been effective in controlling and treating lower gastrointestinal bleeding. Endoscopic bipolar electrocoagulation, radiofrequency ablation, Nd: YAG laser and cryotherapy are possible alternatives to argon, although their evidence level is low. Despite the enormous therapeutic armamentarium, the more severe RP cases may require radiological intervention for lower gastrointestinal bleeding and surgical intervention, especially in complications such as effective control of lower gastrointestinal bleeding, fistulisation, occlusion, and intestinal perforation[3,5,7,8,38,39].
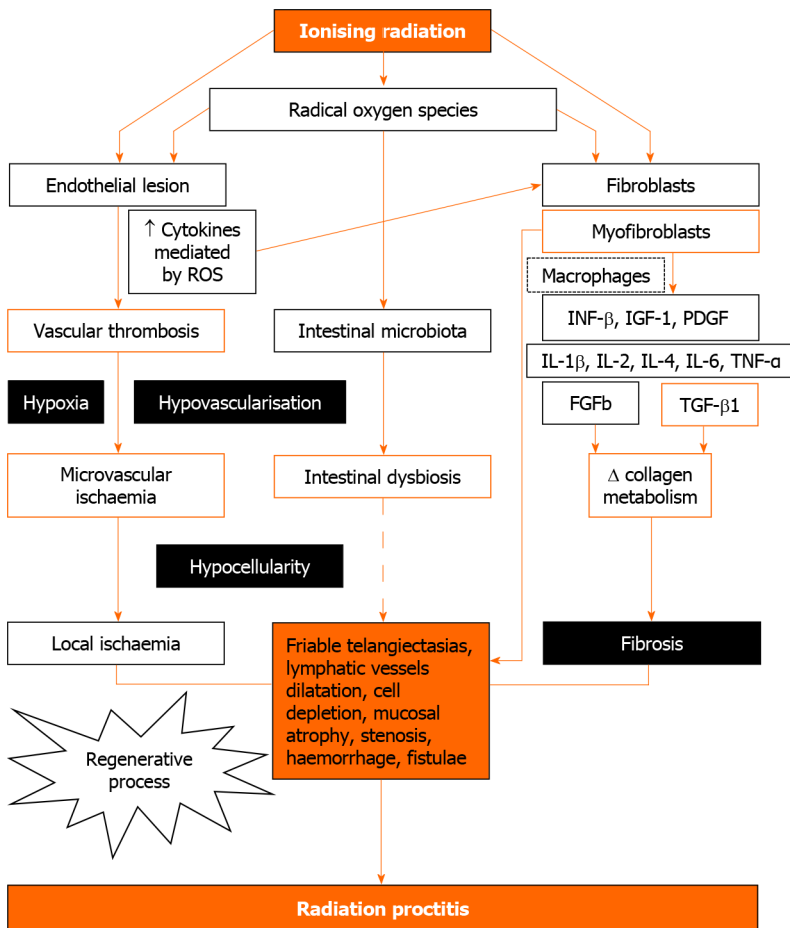
Figure 2 Representative scheme of the several pathophysiological mechanisms involved in radiation proctitis: The hypoxia/hypocellularity/hypovascularisation, intestinal microbiota and the fibroatrophic theories. FGFb: Basic fibroblast growth factor; IGF1: Insulin-like growth factor 1; IL: Interleukin; INF-β: Interferon- beta; PDGF: Platelet-derived growth factor; ROS: Reactive oxygen species; TGF-β1: Transforming growth factor beta-1; TNF-α: Tumour necrosis factor-alpha. Citation: Adapted from Costa DA *et al*[21].

HBOT

HBOT is a treatment based on the inhalation of pure oxygen (100%) in an environment with an atmospheric pressure higher than that existing at sea level (1 atmosphere absolute [ATA]). The HBOT sessions are held inside hermetically sealed hyperbaric chambers, classified as type IIb medical devices (directive 93/42 ECC of June 14, 1993, concerning medical devices). HBOT is used in several clinical conditions as well as in professional and military training. Therapeutic HBOT usually involves pressures higher than 1.4 ATA (141.8 kPa), most frequently ranging between 2.0 (202.6 kPa) and 2.5 ATA (253.3 kPa) for 60 to 120 min[40].

Currently, the ECHM recommends HBOT for the treatment of RP (degree of recommendation I/ level of evidence B)[22]. Unlike most conventional treatment that only alleviated symptoms, HBOT can favourably change the natural history of other RT late sequelae[4]. Its clinical benefit emanates from the therapeutic effects of hyperbaric oxygen that include, among others, the promotion of tissue oxygenation, neovascularisation, reepithelialisation, and the reversal of the fibroatrophic process induced by ionising radiation[16,21,41,42].

The mechanisms that result in HBOT beneficial effects can also cause side effects in some patients, primarily due to pressure and oxygen toxicity. However, when appropriate therapeutics protocols are applied, HBOT is a safe and low-risk intervention, with the adverse events being infrequent and typically not severe[40-43].

In 1991, Charneau *et al*[44] treated the first RP patient with HBOT. The 74-year-old patient had a 5-mo history of transfusion-dependent haemorrhagic RP. For this patient, after the failure of previous treatments (enema with corticosteroids and Nd: YAG laser), HBOT was considered a strategy to avoid surgery. After 82 sessions of HBOT (2.5 ATA, for 90 min, twice daily), a complete clinical response was observed, which remained during the follow-up period of at least 9 mo. After this pioneering

report, others were published, including case reports, retrospective, (non)-randomised studies and clinical trials, as well as several reviews and meta-analyses that studied the clinical impact of HBOT on RP (Table 2)[16,45-71]. However, most studies had both a small number of cases treated and a short follow-up period.

In 1997, Warren *et al*[47] conducted a study with 14 patients undergoing two pressurisation regimens (*n* = 9; 2 ATA, for 120 min, 5-6 times per week; *n* = 5; 2.35 ATA, for 90 min, 5 times per week). The authors documented an overall response rate of 64.3% (57.1% with complete responses) for an average follow-up period of 14.6 (range 2-35) mo. In the same year, Woo *et al*[48], published a study with 18 patients submitted to 24 sessions of HBOT (2 ATA, for 105 min, 6 times per week) with a follow-up period of 14 (range 3-65) mo. In this study, different response rates were reported according to the symptoms analysed: Haemorrhage 41.2% (7/17); rectal pain 50% (2/4); incontinence 75% (3/4) and diarrhoea 50% (4/8). Furthermore, most patients (77.7%) had already undergone other treatments but with little clinical benefit (*n* = 13, enema with corticosteroids; *n* = 1, formalin). Gouëllo *et al*[52], published a study with 36 patients submitted to an average of 67 sessions of HBOT (2.5 ATA, for 90 min, 5 times per week). An overall response rate of 53% (19/36) was observed immediately after the end of treatment. In the 52-mo follow-up period, the overall response rate was 66% (21/32). In 2002, in a systematic review published by Feldmeier and Hampson[2], 14 publications were evaluated in the context of RP and radiation enteritis (12 studies in humans and 2 in animals). Of the 9 studies, 114 patients were considered, and an overall response rate of 95.6% was documented (36%, 41 patients with complete response; 60%, 68 patients with better symptomatic control). Despite these studies have shown an improvement in RP with HBOT, a clinical benefit has also been verified in the small intestine radio-induced malabsorption syndrome. In 2007, Marshall *et al*[16], published the largest study carried out up to that time, with 65 patients with enteritis and RP (85% of patients). The authors described an overall response rate of 68% (43% with complete responses) after at least 30 sessions of HBOT (2.4 ATA, for 90 min, 5 times per week). However, half of the patients (49.2%, 32) had to be submitted to more HBOT sessions, up to a maximum of 60, due to partial response or recurrence of symptoms. The mean follow-up time was 23 (range 1-70) mo. The response rate of patients with low gastrointestinal bleeding was 70%. In those dependent on transfusions, the response rate was very satisfactory since 75% of these patients no longer needed transfusion support. For symptoms other than haemorrhage, the response rate was 58%, with pain reduction, nutritional status improvement, intestinal transit regularisation and even fistulae closure. Moreover, no correlation was established between the treatment response rate and the duration of symptoms or the time between RT and initiation of HBOT.

In 2008, Clarke *et al*[65] published the results of the first multicentre, randomised, sham-controlled, double-blind clinical trial (HORTIS) that included patients with RP refractory to other therapeutic interventions. A total of 150 patients were enrolled, but only 120 completed the study. Patients were randomised to HBOT (Group 1: 2.0 ATA, for 90 min, 5 times per week) or sham treatment with 21% oxygen (Group 2: 1.34-> 1.1 ATA, for 90 min, 5 times per week). The clinical response evaluation was performed after 30 treatment sessions, with the possibility of 10 additional sessions, depending on the investigator's decision. Only 3 patients did not accept the crossover to the active arm of the initial HBOT (Group 1). After adjusting covariates and for an average follow-up period of 2 years, Group 1 significantly improved the mean LENT-SOMA score (5.00 *vs* 2.61, *P* = 0.0019). In the initial allocation phase and after the first efficacy assessment, the experimental group's overall response rate was higher than in the control group (88.9% *vs* 62.5%, *P* = 0.0009). Furthermore, there was also a significant improvement in QoL (pattern of pain, bleeding and intestinal transit) in Group 1 (including in the crossover subgroup of patients). It is noteworthy that, for Group 1, the improvement in QoL in terms of faecal incontinence, faecal urgency, pain and intestinal transit was consistent throughout the follow-up period. In 2015, Tahir *et al* [69] reported an overall response rate of 95% in the 59 patients treated with RP (51% of patients with complete response for a median duration of 15 mo). Bennett *et al*[72], in a Cochrane meta-analysis published in 2016, documented a significant increase in the clinical improvement or even remission of RP after HBOT (relative risk 1.72; 95% confidence interval 1.0-2.9, *P* = 0.04, NNT to benefit 5).

In 2016, Glover *et al*[70], in a multicentre, randomised, double-blind, sham-controlled phase 3 trial (HOT2), evaluated the clinical benefit of HBOT in patients with chronic bowel dysfunction after RT in the context of pelvic neoplasms. Treatment efficacy was determined by comparing the Inflammatory Bowel Disease Questionnaire (IBDQ) and the IBDQ rectal bleeding scores assessed before and 12 mo after starting treatment. Moreover, other secondary endpoints were evaluated: LENT-SOMA, the

Table 2 Summary of the case-series or clinical trials described in the literature regarding the use of hyperbaric oxygen therapy in the treatment of radiation proctitis

Ref.	Study design	Patients (*n*)	RP stages/grades, patients (*n*)	Other (previous) treatments (%)	HBOT protocol	Nº sessions	Overall response rate (%)	Complete response (%)	Follow-up period (mo)
Bouachour *et al*[45], 1990	Retrospective	8	NA	100%	2.5 ATA, 90 min, twice daily (4 wk)-> Once daily	80 ± 10	87.5%	75%	[4-20]
Feldmeier *et al*[46], 1996	Retrospective	7	RTOG/EORTC[36]: 4	28.6%	2.4 ATA, 90 min, 5 ×/wk	24 [3-50]	57%	57%	NA
Warren *et al*[47], 1997	Retrospective	14	Bleeding (*n* = 11); Diarrhoea (*n* = 5); Rectal pain (*n* = 4); Tenesmus (*n* = 2)	78.6%	2.0 ATA, 120 min, 5-6/wk; 2.35 ATA, 90 min, 5 ×/wk	39 [20-72]	64.3%	57.1%	14.6 [2-35]
Woo *et al*[48], 1997	Retrospective	18	Bleeding (*n* = 17); Diarrhoea (*n* = 8); Rectal pain (*n* = 4); Incontinence (*n* = 4)	77.7%	2.0 ATA, 105 min, 6 ×/wk	24 [40]	55.5%; Incontinence 75%; Diarrhoea 50%; Rectal pain 50%; Haemorrhage 41.2%	11.1%; 50%; 25%; 25%; 23.5%	14 [65]
Bredfeldt and Hampson [49], 1998	Retrospective	19	NA	NA	2.36 ATA, 90 min, 5 ×/wk	30	84%	47%	NA
Ugheoke *et al*[50], 1998	Retrospective	8	NA	NA	2.5 ATA, 90 min, 5 ×/wk	28 [20-40]	62.5%	NA	NA
Carl *et al* [51], 1998	Retrospective	2	Bleeding (*n* = 1); Rectal pain (*n* = 1)	NA	2.4 ATA, 90 min, 5 ×/wk	38, 40	50%	50%	NA
Gouëllo *et al*[52], 1999	Retrospective	36	LENT-SOMA: Grade 1 (*n* = 1); Grade 2 (*n* = 11); Grade 3 (*n* = 16); Grade 4 (*n* = 8)	NA	2.5 ATA, 90 min, 5 ×/wk	67 (mean)	66%	25%	52
Kitta *et al* [53], 2000	Retrospective	4	Bleeding (*n* = 3); Rectal pain (*n* = 1)	100%	2.0 ATA, 60 min, 5 ×/wk	37.5 [30-60]	75%	25%	NA
Bem *et al* [54], 2000	Retrospective	2	Dean and Taylor [28]: I-II	100%	2.4 ATA, 90 min, 5 ×/wk	60, 60	100%	100%	[3-48]
Roque *et al* [55], 2001	Retrospective	6	NA	NA	2.5 ATA, 90 min, 5 ×/wk	37 [20-60]	85%	NA	NA
Mayer *et al* [56], 2001	Retrospective	10	RTOG/EORTC[36]: Grade 2 (*n* = 4); Grade 3 (*n* = 6)	Majority (% not stated)	2.2-2.4 ATA, 60 min, 7 ×/wk	28 [13-60]	90%	30%	15.3 [7.5-26.9]
Boyle *et al* [57], 2002	Retrospective	19	NA	NA	2.0 ATA, 120 min, 5 ×/wk	59 [27-80]	68%	NA	NA
Jones *et al* [58], 2006	Retrospective	10	LENT-SOMA: Grade 2 (*n* = 7); Grade 3 (*n* = 3)	100%	2.0-2.5, 90 min, 5 ×/wk	40 [36-41]	77%; Haemorrhage 88.8%; Diarrhoea 80%; Rectal pain 80%	44.4%; 60%; 20%	25 [6-43]
Dall'Era *et al*[59], 2006	Retrospective	27	RTOG/EORTC[36]: 3-4	100%	2.4 ATA, 90 min, 7-7 ×/wk	36 [29-60]	66.6%; Haemorrhage 76%; Rectal pain 75%; Faecal urgency 75%; Rectal ulcer 50%	37%; 48%; 0%; 50%; 21%	13 [1-60]
Fink *et al* [60], 2006	Retrospective	4	NA	100%	2.4 ATA, 90 min, 5 ×/wk	31 [28-37]	75%	25%	33
Girnius *et al*[61], 2006	Retrospective	9	Bleeding Scale for Radiation-Induced	100%	2.5 ATA, 90 min, 5 ×/wk	58 [22-80]	100%	77.7%	17 [1-77]

Study	Design	n	Classification / Symptoms		HBOT protocol	Sessions	Outcomes		Follow-up
			Haemorrhagic Proctitis[33]: Grade 2 (*n* = 1); Grade 3 (*n* = 3); Grade 4 (*n* = 5)						
Marshall *et al*[16], 2007	Retrospective	65 (15 with lesions beyond the rectum)	Bleeding (*n* = 54); Diarrhoea (*n* = 25); Rectal pain (*n* = 25); Tenesmus, urgency, incontinence (*n* = 13); Malnutrition, weight loss (*n* = 7); Bloating, cramping (*n* = 6); Nausea, emesis (*n* = 5); Fistulae (*n* = 2); Total parenteral nutrition (*n* = 2)	65%	2.36 ATA, 90 min, 5 ×/wk	30-> If partial response-> 60	68% (all patients); 65% (rectum); 73% (proximal sites); Haemorrhage 70%; Other symptoms 58% (including pain relief, improved nutritional status and intestinal transit, closure of fistulae)	43%; 39%; 60%; 75%; 33%	23 [1-70]
Sidik *et al* [62,63], 2007	Prospective, randomised clinical trial	HBOT 32; Comparator33	LENT-SOMA: HBOT, mean 7.7 ± 2.0; Control, mean 6.8 ± 2.3. Karnofsky scale: HBOT, mean 73.8 ± 6; Control, mean 74.6 ± 8.3	NA	HBOT, Protocol not reported *vs* Comparator described as "symptomatic treatment"	HBOT, Minimum 18 sessions	Outcomes poorly reported (losses to follow-up, not all patient data provided)	NA	6
Safra *et al* [64], 2008	Retrospective	6	NCI CTCAE[37]: Mean 3.3 [2-4]	100%	2.0 ATA, 90 min, 7 ×/wk	27 [16-40]. Not only RP	100%	16.7%	NA
Clarke *et al* [65], 2008	Randomised, double-blind, sham-controlled, crossover allowed ("HORTIS")	HBOT 76; Comparator74	LENT-SOMA: HBOT, mean 12.55; Sham, mean 12.84	100%	HBOT, 2.0 ATA, 90 min, 5 ×/wk *vs* Sham treatment 1.34-> 1.1 ATA O$_2$ 21%, 90 min, 5 ×/wk	30-> 40	HBOT: 88.9%. Improved bowel-specific and bowel bother and function QoL scores (before crossover) *vs* Sham treatment: 62.5%	HBOT: 7.9% *vs* Sham: 0%	25 [12-60]
Alvaro-Villegas *et al*[66], 2011	Prospective, non-randomised clinical trial	HBOT 17; Comparator14	LENT-SOMA: HBOT, 12.1 ± 2.9; APC, 13.3 ± 2.9	NA	HBOT 2.0-2.5 ATA, 90 min, 5 ×/wk *vs* Non-contact APC, 2.3 mm diameter catheter, 1.6 L/min flow rate at 60 W, mean 3 ± 1 (SD) sessions	HBOT, 35 ± 5 *vs* APC, 3 ± 1	HBOT: 82% *vs* APC: 87%	NA	3
Oliai *et al* [67], 2012	Retrospective	4	LENT-SOMA: Mean 0.66 [0.36-0.93]. Severity of rectal bleeding: Persistent (*n* = 3), Occasional (*n* = 1)	100%	2.0 ATA, 90-105 min, 5 ×/wk	37.5 [30-40]	75%	50%	NA
Carvalho *et al*[68], 2014	Retrospective	30	NA	NA	2.5 ATA, 100 min, 5 ×/wk	66 [38-80]	96.7%	73.3%	NA
Tahir *et al* [69], 2015	Retrospective	59	NA	NA	2.4 ATA, 70 min, 7x/wk	NA	95%	51%	Major response 15 [2-76]. Minor response 20 [1-84]
Glover *et al*[70], 2016	Randomised, double-blind, sham-controlled phase 3 clinical trial ("HOT2")	Ratio 2:1; HBOT 55; Comparator29	LENT-SOMA: Grade 2; Grade 1 with intermittent symptoms. IBDQ bowel function component (n/IQR): HBOT 48 (42-52); Sham 51 (44-59). IBDQ rectal	100%	HBOT 2.4 ATA, 90 min, 5 ×/wk *vs* Sham treatment 1.34 ATA O$_2$ 21%, 90 min, 5 ×/wk	40 (89% of patients) < 38 (11% of patients)	HBOT: IBDQ bowel function component (n/IQR): Δ 3.5 (-3-11). IBDQ rectal bleeding (n/IQR): Δ 3 (1-3) *vs* Sham treatment: IBDQ	NA	13.2 [12.4-14.2]

			bleeding (n/IQR): HBOT 3 (2-4); Sham 3 (2-4). NCI CTCAE [64]: Grade 1-3, 46 (55%). EORTC QLQ-CR38 Question 59: Grade 1-3, 47 (59%)				bowel function component (n/IQR): Δ 4 (-6-9); IBDQ rectal bleeding (n/IQR): Δ 1 (1-2)		
Yoshimizu *et al*[71], 2017	Retrospective	5	Sherman[27]: Grade II (*n* = 3); Grade III (*n* = 1); Grade IV (*n* = 1)	NA	2.5 ATA, 60 min, 5 ×/wk	76 [40-100]	100%	20%	NA

APC: Argon plasma coagulation; ATA: Atmosphere absolute; HBOT: Hyperbaric oxygen therapy; IBDQ: Inflammatory Bowel Disease Questionnaire; IQR: Interquartile range; min, minute; NA: Not available or not applicable; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; O_2: Oxygen; QoL: Quality of life; RP: Radiation proctitis; SD: Standard deviation; Δ: Median change from baseline to 12 mo.

11-question questionnaire related to symptoms selected from the CTCAE gastro-intestinal scale (version 4.0) and QoL through validated questionnaires (Questionnaire basic EORTC QLQ-C30 and colorectal module QLQ-CR38). Patients of both sexes with ages over 18 years were included, with at least grade 2 gastrointestinal symptoms of any category of LENT-SOMA or grade 1 with intermittent symptoms due to RT performed at least 12 mo before in the context of rectal, prostate, testicle, bladder, cervix, vagina, vulva or ovary neoplasms. Patients with grade 3 symptoms LENT-SOMA were excluded since they have higher affectation on activities of daily living and require, generally, more aggressive treatments. Patients with RT symptoms were considered eligible for the trial only if they had been submitted to other general interventions for at least 3 mo (*e.g.*, diet change, oral therapeutic optimisation) with no improvement. Patients were randomised in a 2:1 ratio in favour of HBOT and stratified by centre. Patients were randomised to HBOT (2.4 ATA, for 90 min, 5 times per week) or 21% oxygen (1.3 ATA, for 90 min, 5 times per week). Of the 84 patients included in this clinical trial, 55 underwent HBOT and 29 sham treatment. In the analysis of clinical efficacy, no difference was identified between the two arms, when comparing the main endpoints: IBDQ bowel component [HBOT = 46; sham treatment = 23; HBOT: 4 (-3 to 11) *vs* sham treatment: 4 (-6 to 9), *P* = 0.50] and IBDQ rectal bleeding [HBOT = 29; sham treatment = 11; HBOT: 3 (1 to 3) *vs* sham treatment: 1 (1 to 2), *P* = 0.092].

The results of the HOT2 clinical trial are inconsistent with most previous clinical evidence, including the Cochrane meta-analysis[72], primarily based on the HORTIS [65] clinical trial. The HOT2 study[70] is a very relevant clinical trial from a methodo-logical point of view: Phase 3, randomisation 2:1, stratification by centre, double-blind, sham-controlled, with primary and secondary endpoints with previously validated scores and questionnaires and with well-defined inclusion/exclusion criteria, in-cluding a period of at least 3 mo for possible symptom optimisation and control. However, one can enumerate some aspects that can be criticised (not only exclusively for this trial): (1) The sample size is debatable for a phase 3 clinical trial when it is supposed to comprises a total number of patients over 300. The statistical calculation was based on assumptions defined and validated in previous studies. However, the comparison between the two arms was performed with an insufficient number of patients (HBOT: 46 *vs* sham treatment: 23); (2) The drop-out rate was 17.86% (15 patients: 9 from the HBOT group and 6 from sham treatment), with only 69 out of 84 patients having a 12-mo follow-up period. The final statistical power was 75%, although the study had been designed for 80% power; (3) Patients with symptoms ≥ grade 3 LENT-SOMA (*e.g.*, severe faecal incontinence or transfusion-dependent RP) were not included. Thus, one cannot generalise the results for this subgroup; (4) It is unknown whether the percentage of patients with a medical history of lower gastrointestinal bleeding influences their progress during the study (HBOT: 62% *vs* sham treatment: 79%); (5) The dietary and/or pharmacological measures performed in the period prior to randomisation were not discriminated (*e.g.*, diet type, probiotics, antibiotic cycles). Did these different procedures influence the natural history of the disease and the potential response to treatment? (6) The smoking habits of the patients were not quantified. Otto *et al*[73], in a study on diabetic foot, determined that patients with above a 10 pack-year (P-Y) history of smoking would need an average of more than 8 to 14 sessions of HBOT to obtain the same therapeutic effect as non-smokers. Freiberger *et al*[74] reported that in patients with mandible osteoradionecrosis, those who smoked showed a shorter maintained treatment period response to HBOT when compared to non-smoking patients (15.8 *vs* 86.1 mo). The stratification by smoking
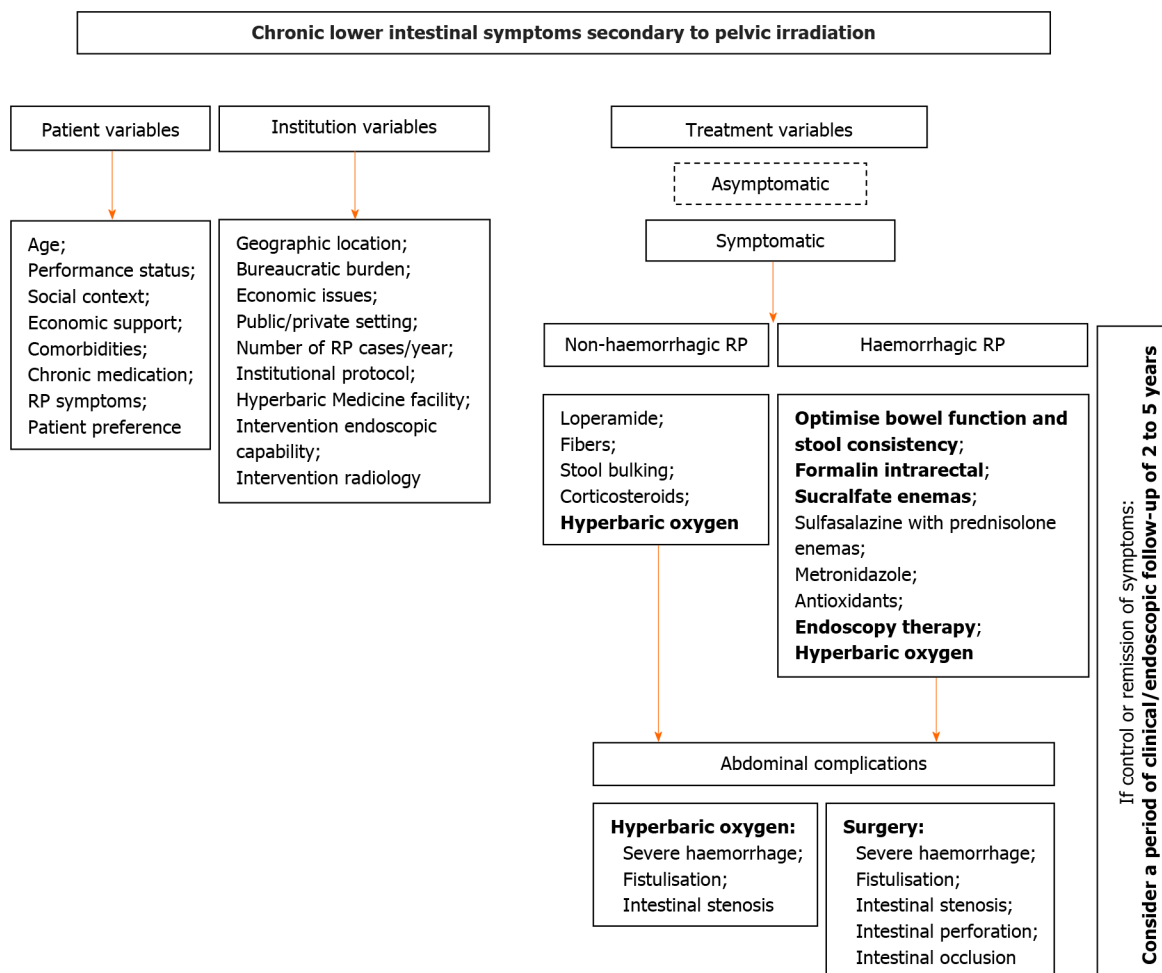
Figure 3 Suggested treatment algorithm for radiation proctitis based on variables related to the patient, institution, and the severity of the clinical context. RP: Radiation proctitis; RT: Radiotherapy.

habits could have been relevant in this trial (non-smoker or smoker ≤10 P-Y *vs* >10 P-Y); (7) The distribution of the subgroup of patients (*n* = 9; 11%) who did not complete the 40 treatment sessions in both arms of the clinical trial is unknown; (8) The endoscopic response to the recommended treatments is unknown; (9) The clinical and endoscopic evolution beyond the median follow-up period 13.2 (range 12.4-14.2) is also unknown. In HORTIS clinical trial[65] it was observed and additional and maintained response beyond 12 mo of the follow-up period; and (10) The absence of a third arm in the study comparing HBOT to another conventional treatment for RP.

We recommend that HBOT, combined with nutritional support and local treatment, may be beneficial for patients with moderate to severe symptoms that do not require surgical intervention. The HBOT regimen should include at least 20-30 sessions with a pressure of 2 to 2.5 ATA for 60 to 120 min/d to ensure a more effective clinical response. The treatment protocol total duration may be extended to several weeks until a clinical and radiological complete response is obtained, and the follow-up should be personalised to each clinical context, considering a period of 2 to 5 years (Figure 3).

CONCLUSION

Although there are several effective therapeutic strategies to treat RP and improve its clinical condition, gold standard management has not yet been established. RP's management approach must be personalised according to the patient, clinical condition severity, and the institution's experience. The most conservative treatment comprises diet modulation and nutritional support, oral and intrarectal pharmaco-logical treatment and HBOT. Endoscopic treatment may be indicated for the control and treatment of lower gastrointestinal bleeding. In severe refractory disease with

complications, surgical intervention should be considered.

During HBOT, the occurrence of adverse events is relatively infrequent. HBOT may potentially alleviate gastrointestinal radio-induced complications, including rectal bleeding, diarrhoea and pain. The authors' expectancies are that, in the near future, the controversy regarding HBOT in RP will be dimmed. More prospective and randomised studies are needed to validate the effectiveness of HBOT in the 'real-world' clinical practice.

REFERENCES

1   **Cancer Tomorrow**.   Global Cancer Observatory. [cited 1 February 2021]. Available from: https://gco.iarc.fr/tomorrow/graphic-isotype?type=1&population=900&mode=population&sex=0&cancer=39&age_group=value&apc_male=0&apc_female=0

2   **Feldmeier JJ**, Hampson NB. A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach. *Undersea Hyperb Med* 2002; **29**: 4-30 [PMID: 12507182]

3   **Alberto SF**, Félix J, Pires S, Pires E, Figueiredo A, Gorjão R, Alves N, Ramos de Deus J. Proctopatia rádica – Experiência de um serviço em terapêutica endoscópica com árgon plasma. *Revista Portuguesa de Coloproctologia* 2006; **3**: 6-13

4   **Pasquier D**, Schmutz J, Lartigau E (Ed.   ): Handbook on Hyperbaric Medicine; Dordrecht, The Netherlands, Springer, 2006

5   **Hauer-Jensen M**, Denham JW, Andreyev HJ. Radiation enteropathy--pathogenesis, treatment and prevention. *Nat Rev Gastroenterol Hepatol* 2014; **11**: 470-479 [PMID: 24686268 DOI: 10.1038/nrgastro.2014.46]

6   **Haddock MG**, Sloan JA, Bollinger JW, Soori G, Steen PD, Martenson JA; North Central Cancer Treatment Group. Patient assessment of bowel function during and after pelvic radiotherapy: results of a prospective phase III North Central Cancer Treatment Group clinical trial. *J Clin Oncol* 2007; **25**: 1255-1259 [PMID: 17401014 DOI: 10.1200/JCO.2006.09.0001]

7   **Friedman LS**, Hong TS.   Clinical manifestations, diagnosis, and treatment of radiation proctitis" Willett CG, & Grover S (Eds.). UpToDate. [cited 1 February 2021]. Available from: https://www.uptodate.com/contents/clinical-manifestations-diagnosis-and-treatment-of-radiation-proctitis

8   **Pal N**.   Radiation Enteritis and Proctitis" Geibel J (Ed.). Medscape. [cited 1 February 2021]. Available from: https://emedicine.medscape.com/article/197483-overview

9   **Shadad AK**, Sullivan FJ, Martin JD, Egan LJ. Gastrointestinal radiation injury: symptoms, risk factors and mechanisms. *World J Gastroenterol* 2013; **19**: 185-198 [PMID: 23345941 DOI: 10.3748/wjg.v19.i2.185]

10 **Agrawal PP**, Bansal N, Bahadur AK, Singh K, Rathi AK. Management of chronic hemorrhagic radiation proctitis. *Asia-Pac J Clin Onco* 2007; **3**: 19-29 [DOI: 10.1111/j.1743-7563.2006.00084.x]

11 **Bentzen SM**, Dörr W, Anscher MS, Denham JW, Hauer-Jensen M, Marks LB, Williams J. Normal tissue effects: reporting and analysis. *Semin Radiat Oncol* 2003; **13**: 189-202 [PMID: 12903009 DOI: 10.1016/S1053-4296(03)00036-5]

12 **Cooper JS**, Hanley ME.   Hyperbaric Treatment Of Radiation Proctitis. 2020 Aug 15. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan– [PMID: 30726028]

13 **Yeoh EK**, Horowitz M. Radiation enteritis. *Surg Gynecol Obstet* 1987; **165**: 373-379 [PMID: 3310287]

14 **Abayomi J**, Kirwan J, Hackett A. The prevalence of chronic radiation enteritis following radiotherapy for cervical or endometrial cancer and its impact on quality of life. *Eur J Oncol Nurs* 2009; **13**: 262-267 [PMID: 19640788 DOI: 10.1016/j.ejon.2009.02.007]

15 **Andreyev J**. Gastrointestinal complications of pelvic radiotherapy: are they of any importance? *Gut* 2005; **54**: 1051-1054 [PMID: 16009675 DOI: 10.1136/gut.2004.062596]

16 **Marshall GT**, Thirlby RC, Bredfeldt JE, Hampson NB. Treatment of gastrointestinal radiation injury with hyperbaric oxygen. *Undersea Hyperb Med* 2007; **34**: 35-42 [PMID: 17393937]

17 **Do NL**, Nagle D, Poylin VY. Radiation proctitis: current strategies in management. *Gastroenterol Res Pract* 2011; **2011**: 917941 [PMID: 22144997 DOI: 10.1155/2011/917941]

18 **Michalski JM**, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation dose-volume effects in radiation-induced rectal injury. *Int J Radiat Oncol Biol Phys* 2010; **76**: S123-S129 [PMID: 20171506 DOI: 10.1016/j.ijrobp.2009.03.078]

19 **Marx RE**. Osteoradionecrosis: a new concept of its pathophysiology. *J Oral Maxillofac Surg* 1983; **41**: 283-288 [PMID: 6572704 DOI: 10.1016/0278-2391(83)90294-x]

20 **Delanian S**, Lefaix JL. [Mature bone radionecrosis: from recent physiopathological knowledge to an innovative therapeutic action]. *Cancer Radiother* 2002; **6**: 1-9 [PMID: 11899674 DOI: 10.1016/s1278-3218(01)00142-1]

21 **Costa DA**, Costa TP, Netto EC, Joaquim N, Ventura I, Pratas AC, Winckler P, Silva IP, Pinho AC, Sargento IG, Guerreiro FG, Moreira AR. New perspectives on the conservative management of osteoradionecrosis of the mandible: A literature review. *Head Neck* 2016; **38**: 1708-1716 [PMID:

27240248 DOI: 10.1002/hed.24495]

22 **Mathieu D**, Marroni A, Kot J. Tenth European Consensus Conference on Hyperbaric Medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. *Diving Hyperb Med* 2017; **47**: 24-32 [PMID: 28357821 DOI: 10.28920/dhm47.1.24-32]

23 **Kumagai T**, Rahman F, Smith AM. The Microbiome and Radiation Induced-Bowel Injury: Evidence for Potential Mechanistic Role in Disease Pathogenesis. *Nutrients* 2018; **10** [PMID: 30279338 DOI: 10.3390/nu10101405]

24 **Indaram AV**, Visvalingam V, Locke M, Bank S. Mucosal cytokine production in radiation-induced proctosigmoiditis compared with inflammatory bowel disease. *Am J Gastroenterol* 2000; **95**: 1221-1225 [PMID: 10811331 DOI: 10.1111/j.1572-0241.2000.02013.x]

25 **Symon Z**, Goldshmidt Y, Picard O, Yavzori M, Ben-Horin S, Alezra D, Barshack I, Chowers Y. A murine model for the study of molecular pathogenesis of radiation proctitis. *Int J Radiat Oncol Biol Phys* 2010; **76**: 242-250 [PMID: 20005457 DOI: 10.1016/j.ijrobp.2009.07.1736]

26 **Gerassy-Vainberg S**, Blatt A, Danin-Poleg Y, Gershovich K, Sabo E, Nevelsky A, Daniel S, Dahan A, Ziv O, Dheer R, Abreu MT, Koren O, Kashi Y, Chowers Y. Radiation induces proinflammatory dysbiosis: transmission of inflammatory susceptibility by host cytokine induction. *Gut* 2018; **67**: 97-107 [PMID: 28438965 DOI: 10.1136/gutjnl-2017-313789]

27 **Sherman LF**. A reevaluation of the factitial proctitis problem. *Am J Surg* 1954; **88**: 773-779 [PMID: 13197684 DOI: 10.1016/0002-9610(54)90274-3]

28 **Dean RE**, Taylor ES. Surgical treatment of complications resulting from irradiation therapy of cervical cancer. *Am J Obstet Gynecol* 1960; **79**: 34-42 [PMID: 13815162 DOI: 10.1016/0002-9378(60)90360-4]

29 **Gilinsky NH**, Burns DG, Barbezat GO, Levin W, Myers HS, Marks IN. The natural history of radiation-induced proctosigmoiditis: an analysis of 88 patients. *Q J Med* 1983; **52**: 40-53 [PMID: 6603628]

30 **Langberg CW**, Sauer T, Reitan JB, Hauer-Jensen M. Tolerance of rat small intestine to localized single dose and fractionated irradiation. *Acta Oncol* 1992; **31**: 781-787 [PMID: 1476759 DOI: 10.3109/02841869209083871]

31 **Chutkan R**, Lipp A, Waye J. The argon plasma coagulator: a new and effective modality for treatment of radiation proctitis. *Gastrointest Endosc* 1997; **45**: AB27 [DOI: 10.1016/S0016-5107(97)80012-0]

32 **Wachter S**, Gerstner N, Goldner G, Pötzi R, Wambersie A, Pötter R. Endoscopic scoring of late rectal mucosal damage after conformal radiotherapy for prostatic carcinoma. *Radiother Oncol* 2000; **54**: 11-19 [PMID: 10719695 DOI: 10.1016/s0167-8140(99)00173-5]

33 **Zinicola R**, Rutter MD, Falasco G, Brooker JC, Cennamo V, Contini S, Saunders BP. Haemorrhagic radiation proctitis: endoscopic severity may be useful to guide therapy. *Int J Colorectal Dis* 2003; **18**: 439-444 [PMID: 12677457 DOI: 10.1007/s00384-003-0487-y]

34 **Chi KD**, Ehrenpreis ED, Jani AB. Accuracy and reliability of the endoscopic classification of chronic radiation-induced proctopathy using a novel grading method. *J Clin Gastroenterol* 2005; **39**: 42-46 [PMID: 15599209]

35 **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**: 1-8 [PMID: 15690650 DOI: 10.1007/s10350-004-0821-7]

36 **Cox JD**, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995; **31**: 1341-1346 [PMID: 7713792 DOI: 10.1016/0360-3016(95)00060-C]

37 **NCI CTCAE version 5.0**. National Cancer Institute (2017) Common Terminology Criteria for Adverse Events (CTCAE) 5.0. [cited 1 February 2021]. Available from: https://ctep.cancer.gov/protoc olDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

38 **Paquette IM**, Vogel JD, Abbas MA, Feingold DL, Steele SR; Clinical Practice Guidelines Committee of The American Society of Colon and Rectal Surgeons. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Treatment of Chronic Radiation Proctitis. *Dis Colon Rectum* 2018; **61**: 1135-1140 [PMID: 30192320 DOI: 10.1097/DCR.0000000000001209]

39 **Ranna V**, Cheng KKF, Castillo DA, Porcello L, Vaddi A, Lalla RV, Bossi P, Elad S; Mucositis Study group of the Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO). Development of the MASCC/ISOO clinical practice guidelines for mucositis: an overview of the methods. *Support Care Cancer* 2019; **27**: 3933-3948 [PMID: 31286227 DOI: 10.1007/s00520-019-04891-1]

40 **Costa DA**, Ganilha JS, Barata PC, Guerreiro FG. Seizure frequency in more than 180,000 treatment sessions with hyperbaric oxygen therapy - a single centre 20-year analysis. *Diving Hyperb Med* 2019; **49**: 167-174 [PMID: 31523791 DOI: 10.28920/dhm49.3.167-174]

41 **Albuquerque e Sousa JG**. A medicina hiperbárica. Uma especificidade da medicina naval. *Revista da Armada* 2006

42 **Fernandes TD**. [Hyperbaric medicine]. *Acta Med Port* 2009; **22**: 323-334 [PMID: 19909659]

43 **Jokinen-Gordon H**, Barry RC, Watson B, Covington DS. A Retrospective Analysis of Adverse Events in Hyperbaric Oxygen Therapy (2012-2015): Lessons Learned From 1.5 Million Treatments. *Adv Skin Wound Care* 2017; **30**: 125-129 [PMID: 28198743 DOI: 10.1097/01.ASW.0000508712.86959.c9]

44   **Charneau J**, Bouachour G, Person B, Burtin P, Ronceray J, Boyer J. Severe hemorrhagic radiation proctitis advancing to gradual cessation with hyperbaric oxygen. *Dig Dis Sci* 1991; **36**: 373-375 [PMID: 1995275 DOI: 10.1007/BF01318212]

45   **Bouachour G**, Ronceray J, Bouali AB, Person B, Boyer J, Alquier Ph.   Hyperbaric oxygen in the treatment of radiation induced proctitis: A report on 8 cases. Proceedings of the Tenth International Congress on Hyperbaric Medicine, Amsterdam, 1990: 158–163

46   **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**: 205-213 [PMID: 8989850]

47   **Warren DC**, Feehan P, Slade JB, Cianci PE. Chronic radiation proctitis treated with hyperbaric oxygen. *Undersea Hyperb Med* 1997; **24**: 181-184 [PMID: 9308141]

48   **Woo TC**, Joseph D, Oxer H. Hyperbaric oxygen treatment for radiation proctitis. *Int J Radiat Oncol Biol Phys* 1997; **38**: 619-622 [PMID: 9231688 DOI: 10.1016/s0360-3016(97)00017-5]

49   **Bredfeldt JE**, Hampson NB. Hyperbaric oxygen (HBO2) therapy for chronic radiation enteritis. *Am J Gastroenterol* 1998; **93**: 1665

50   **Ugheoke EA**, Norris T, Sharma VK, Vasudeva R.   Radiation proctitis (RTP): Is there a role for hyperbaric oxygen (HBO) therapy? Proceedings of the American College of Gastroenterology 63rd Annual Scientific Meeting, October 12–14, 1998, Boston, MA

51   **Carl UM**, Peusch-Dreyer D, Frieling T, Schmitt G, Hartmann KA. Treatment of radiation proctitis with hyperbaric oxygen: what is the optimal number of HBO treatments? *Strahlenther Onkol* 1998; **174**: 482-483 [PMID: 9765691 DOI: 10.1007/BF03038628]

52   **Gouëllo JP**, Bouachour G, Person B, Ronceray J, Cellier P, Alquier P. [The role of hyperbaric oxygen therapy in radiation-induced digestive disorders. 36 cases]. *Presse Med* 1999; **28**: 1053-1057 [PMID: 10394370]

53   **Kitta T**, Shinohara N, Shirato H, Otsuka H, Koyanagi T. The treatment of chronic radiation proctitis with hyperbaric oxygen in patients with prostate cancer. *BJU Int* 2000; **85**: 372-374 [PMID: 10671898 DOI: 10.1046/j.1464-410x.2000.00404.x]

54   **Bem J**, Bem S, Singh A. Use of hyperbaric oxygen chamber in the management of radiation-related complications of the anorectal region: report of two cases and review of the literature. *Dis Colon Rectum* 2000; **43**: 1435-1438 [PMID: 11052522 DOI: 10.1007/BF02236641]

55   **Roque F**, Saraiva A, Simão G.   Hyperbaric oxygen therapy for late radio-induced intestinal lesions. Proceedings of the European Society for Therapeutic Radiology and Consensus Conference, Lisbon, Portugal, 2001: 105–121

56   **Mayer R**, Klemen H, Quehenberger F, Sankin O, Mayer E, Hackl A, Smolle-Juettner FM. Hyperbaric oxygen--an effective tool to treat radiation morbidity in prostate cancer. *Radiother Oncol* 2001; **61**: 151-156 [PMID: 11690680 DOI: 10.1016/s0167-8140(01)00430-3]

57   **Boyle BR**, Moon RE, Stolp BW, Dear G de L, Kraft KL, Piantadosi CA. Hyperbaric oxygen therapy for chronic radiation proctitis (CRP) [Abstract]. *Undersea Hyperb Med* 2002; **29** (Suppl): 19

58   **Jones K**, Evans AW, Bristow RG, Levin W. Treatment of radiation proctitis with hyperbaric oxygen. *Radiother Oncol* 2006; **78**: 91-94 [PMID: 16337705 DOI: 10.1016/j.radonc.2005.11.004]

59   **Dall'Era MA**, Hampson NB, Hsi RA, Madsen B, Corman JM. Hyperbaric oxygen therapy for radiation induced proctopathy in men treated for prostate cancer. *J Urol* 2006; **176**: 87-90 [PMID: 16753375 DOI: 10.1016/S0022-5347(06)00491-5]

60   **Fink D**, Chetty N, Lehm JP, Marsden DE, Hacker NF. Hyperbaric oxygen therapy for delayed radiation injuries in gynecological cancers. *Int J Gynecol Cancer* 2006; **16**: 638-642 [PMID: 16681739 DOI: 10.1111/j.1525-1438.2006.00388.x]

61   **Girnius S**, Cersonsky N, Gesell L, Cico S, Barrett W. Treatment of refractory radiation-induced hemorrhagic proctitis with hyperbaric oxygen therapy. *Am J Clin Oncol* 2006; **29**: 588-592 [PMID: 17148996 DOI: 10.1097/01.coc.0000236004.95384.5b]

62   **Sidik S**, Hardjodisastro D, Setiabudy R, Gondowiardjo S. Does hyperbaric oxygen administration decrease side effect and improve quality of life after pelvic radiation? *Acta Med Indones* 2007; **39**: 169-173 [PMID: 18046062]

63   **Sidik S**, Hardjodisastro D, Setiabudy R, Gondowiardjo S, Yuwono V. Oxygen hyperbaric therapy in patients with radiation proctitis. *Indones J Gastroenterol Hepatol Dig Endosc* 2007; **8**: 1-4

64   **Safra T**, Gutman G, Fishlev G, Soyfer V, Gall N, Lessing JB, Almog R, Matcievsky D, Grisaru D. Improved quality of life with hyperbaric oxygen therapy in patients with persistent pelvic radiation-induced toxicity. *Clin Oncol (R Coll Radiol)* 2008; **20**: 284-287 [PMID: 18222656 DOI: 10.1016/j.clon.2007.12.005]

65   **Clarke RE**, Tenorio LM, Hussey JR, Toklu AS, Cone DL, Hinojosa JG, Desai SP, Dominguez Parra L, Rodrigues SD, Long RJ, Walker MB. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. *Int J Radiat Oncol Biol Phys* 2008; **72**: 134-143 [PMID: 18342453 DOI: 10.1016/j.ijrobp.2007.12.048]

66   **Alvaro-Villegas JC**, Sobrino-Cossío S, Tenorio-Téllez LC, de la Mora-Levy JG, Hernández-Guerrero A, Alonso-Lárraga JO, Vela-Chávez T. Argon plasma coagulation and hyperbaric oxygen therapy in chronic radiation proctopathy, effectiveness and impact on tissue toxicity. *Rev Esp Enferm Dig* 2011; **103**: 576-581 [PMID: 22149559 DOI: 10.4321/s1130-01082011001100004]

67   **Oliai C**, Fisher B, Jani A, Wong M, Poli J, Brady LW, Komarnicky LT. Hyperbaric oxygen therapy for radiation-induced cystitis and proctitis. *Int J Radiat Oncol Biol Phys* 2012; **84**: 733-740 [PMID:

22440041 DOI: 10.1016/j.ijrobp.2011.12.056]

68   **Carvalho TM**, Magro C, Anão A, Guerreiro F.   Hyperbaric Oxygen treatment in radiation induced proctitis: four years experience in the Portuguese Navy Hyperbaric Medical Center. 40th Annual Meeting of European Underwater and Baromedical Society (EUBS), Wiesbaden, Germany, 2014

69   **Tahir AR**, Westhuyzen J, Dass J, Collins MK, Webb R, Hewitt S, Fon P, McKay M. Hyperbaric oxygen therapy for chronic radiation-induced tissue injuries: Australasia's largest study. *Asia Pac J Clin Oncol* 2015; **11**: 68-77 [PMID: 25382755 DOI: 10.1111/ajco.12289]

70   **Glover M**, Smerdon GR, Andreyev HJ, Benton BE, Bothma P, Firth O, Gothard L, Harrison J, Ignatescu M, Laden G, Martin S, Maynard L, McCann D, Penny CEL, Phillips S, Sharp G, Yarnold J. Hyperbaric oxygen for patients with chronic bowel dysfunction after pelvic radiotherapy (HOT2): a randomised, double-blind, sham-controlled phase 3 trial. *Lancet Oncol* 2016; **17**: 224-233 [PMID: 26703894 DOI: 10.1016/S1470-2045(15)00461-1]

71   **Yoshimizu S**, Chino A, Miyamoto Y, Tagao F, Iwasaki S, Ide D, Tamegai Y, Igarashi M, Saito S, Fujisaki J. Efficacy of hyperbaric oxygen therapy in patients with radiation-induced rectal ulcers: Report of five cases. *Dig Endosc* 2017; **29**: 718-722 [PMID: 28349612 DOI: 10.1111/den.12880]

72   **Bennett MH**, Feldmeier J, Hampson NB, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. *Cochrane Database Syst Rev* 2016; **4**: CD005005 [PMID: 27123955 DOI: 10.1002/14651858.CD005005.pub4]

73   **Otto GH**, Buyukcakir C, Fife CE. Effects of smoking on cost and duration of hyperbaric oxygen therapy for diabetic patients with non-healing wounds. *Undersea Hyperb Med* 2000; **27**: 83-89 [PMID: 11011798]

74   **Freiberger JJ**, Yoo DS, de Lisle Dear G, McGraw TA, Blakey GH, Padilla Burgos R, Kraft K, Nelson JW, Moon RE, Piantadosi CA. Multimodality surgical and hyperbaric management of mandibular osteoradionecrosis. *Int J Radiat Oncol Biol Phys* 2009; **75**: 717-724 [PMID: 19328634 DOI: 10.1016/j.ijrobp.2008.11.025]

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