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
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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 gastrointestinal 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 vulnerable 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 and treatment.

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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.
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 intraabdominal 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 1/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 mucusitis that interferes with the intestinal barrier’s function, allowing antigen translocation including microorganisms[23]. If the submucosa
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].
| Ref. | Stages/grades | Description                                                                 |
|------|--------------|-----------------------------------------------------------------------------|
| Sherman[37], 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 peri-proctitis, marked pain, and sensitivity; II: Presence of ulceration with a greyish tenacious slough, usually involving the anterior rectal wall, and proctitis with grade 1 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, 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 hyalised 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 polygonal epithelium 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 (RPASS) | 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—factors that influence 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: Obstructive or bleeding requiring surgery; 4: Necrosis, perforation, or fistulae; 5: Death related to adverse event. |
| NCI CTC AE 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 anti-diarrheal 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].
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
Hyperbaric oxygen and radiation proctitis was 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[33], 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[57], 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%; 23.3% | 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[30], 1988 | 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 |
| Gouëlle 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 |
| Bern 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] |
| Authors            | Study Design                          | Sample Size | Characteristics | HBOT Parameters | LENT-SOMA | HBOT Parameters | HBOT Parameters | Outcomes |
|--------------------|---------------------------------------|-------------|-----------------|-----------------|------------|----------------|----------------|-----------|
| Marshall et al.    | Retrospective                         | 65 (15 with lesions beyond the rectum) |                 | 2.4 ATA, 70 min, 5 ×/wk | 30.3 | 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) |
| Sidik et al. [62,63], 2007 | Prospective, randomised clinical trial | HBOT 32; Comparator 33 | NA | HBOT, Protocol not reported vs Comparator described as “symptomatic treatment” | 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; Comparator 74 | NA | HBOT, 2.0 ATA, 90 min, 5 ×/wk vs Sham, mean 12.84 | 30.4 | ≥ 40 | 100% | 25 [12-60] |
| Alvaro-Villegas et al. [66], 2011 | Prospective, non-randomised clinical trial | HBOT 17; Comparator 14 | 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 (5D) sessions | 35 ± 3 vs APC, 3 ± 1 | HBOT: 82% vs APC: 87% | NA | 3 |
| Olai et al. [67], 2012 | Retrospective                          | 4           | NA | LENT-SOMA: Mean 0.66 [0.36-0.93], Severity of rectal bleeding: Persistent (n = 5), Occasional (n = 1) | 2.0 ATA, 90-105 min, 5 ×/wk | 37.5 [30-40] | 75% | 50% | NA |
| Carvalho et al. [68], 2014 | Retrospective                          | 30          | NA | HBOT, 2.0-2.5 ATA, 90 min, 5 ×/wk vs Sham treatment 1.54-1.1 ATA O2; 21%, 90 min, 5 ×/wk | 35 ± 3 vs APC, 3 ± 1 | HBOT: 82% vs APC: 87% | NA | 3 |
| Tahir et al. [69], 2015 | Retrospective                          | 59          | NA | LENT-SOMA: Grade 2; Grade 1 with intermittent symptoms. IBDO bowel function component (n/IQR); HBOT 48 (42-52); Sham 51 (44-59), IBDO rectal | HBOT 2.4 ATA, 90 min, 5 ×/wk vs Sham treatment 1.34-1.14 ATA O2; 21% | 40 (89% of patients) < 38 (11% of patients) vs Sham treatment: IBDO 13.2 [12.4-14.2] | NA | 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; Comparator 29 | NA | HBOT 2.4 ATA, 90 min, 5 ×/wk vs Sham treatment 1.34-1.14 ATA O2; 21% | 40 (89%) of patients | 75% | 50% | NA |

HBOT: Hyperbaric Oxygen Therapy; IBDQ: Inflammatory Bowel Disease Questionnaire; RP: Response Rate; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; LENT-SOMA: Lee Enneman bowel scale; APC: Autologous Platelet Concentrate; IQR: Interquartile Range; SD: Standard Deviation; IBD: Inflammatory Bowel Disease; O2: Oxygen.
11-question questionnaire related to symptoms selected from the CTCAE gastrointestinal 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 methodological 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, including 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
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 pharmacological 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.

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