



# The role of hyperbaric oxygen therapy in the treatment of radiation lesions

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Received: 4 April 2022 / Accepted: 14 July 2022

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## Abstract

**Introduction** Cancer remains one of the leading causes of death worldwide, with 50–60% of patients requiring radiotherapy during the course of treatment. Patients' survival rate has increased significantly, with an inevitable increase in the number of patients experiencing side effects from cancer therapy. One such effect is late radiation injuries in which hyperbaric oxygen therapy appears as complementary treatment. With this work we intend to divulge the results of applying hyperbaric oxygen therapy among patients presenting radiation lesions in our Hyperbaric Medicine Unit.

**Materials and methods** Retrospective analysis of clinical records of patients with radiation lesions treated at the Hyperbaric Medicine Unit assessed by the scale Late Effects of Normal Tissues—Subjective, Objective, Management, Analytical (LENT-SOMA) before and after treatment, between October 2014 and September 2019 were included. Demographic characteristics, primary tumor site, subjective assessment of the LENT-SOMA scale before and after treatment were collected and a comparative analysis (Students *t* test) was done.

**Results** 88 patients included: 33 with radiation cystitis, 20 with radiation proctitis, 13 with osteoradionecrosis of the mandible and 22 with radiation enteritis. In all groups, there was a significant decrease ( $p < 0.005$ ) in the subjective parameter of the LENT-SOMA scale.

**Discussion** Late radiation lesions have a major influence on patients' quality of life. In our study hyperbaric oxygen therapy presents as an effective therapy after the failure of conventional treatments.

**Conclusion** Hyperbaric oxygen therapy is an effective complementary therapy in the treatment of refractory radiation lesions.

**Keywords** Hyperbaric oxygen therapy · Radiation induced · Cystitis · Osteoradionecrosis · Proctitis

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## Introduction

Cancer remains one of the leading causes of death worldwide [1]. According to GLOBOCAN, in 2020, 60467 new cancer cases occurred in Portugal and it is estimated that these numbers will keep increasing until 2025 [2]. Currently, 50–60% of cancer patients will have radiotherapy at some point in the course of their disease, but it is estimated that this percentage will increase by approximately 15% in the upcoming years [3].

The therapeutic approach of oncological patients may involve multimodal treatments such as surgery, radiotherapy, chemotherapy, immunotherapy and/or target therapy.

With the emergence of these therapeutic options, survival rates of oncological patients have been increasing significantly, creating a high number of long-survivors. This progress led to an inevitable increase in the number of patients experiencing side effects of the oncological therapeutic used,

in some cases with a negative impact on their quality of life [4]

Radiotherapy consists of applying ionizing radiation on biological tissues, with a therapeutic goal. The use of this ionizing radiation in clinical practice began shortly after Wilhelm Röntgen found the X radiation in 1895. The impressive technical progression over the last years and the emergence of high precision treatment modalities have allowed for a better tumor control with less toxicities. As a therapeutic modality, radiotherapy may be administered either with an intention to cure (radical, neoadjuvant or adjuvant) or as a palliative treatment (for pain relief, hemostatic, decompressive, or in the treatment of brain, pulmonary, or hepatic metastases, among others). It can be delivered as monotherapy or combined with radiosensitizing chemotherapy. Generally, radiotherapy treatments are divided into two groups according to how the radiation is delivered—In External Radiotherapy, the source of radiation (linear accelerator) is at a certain distance of the patient, whereas in Brachytherapy radioactive sources are put inside the tumor (e.g. prostate), directly in contact with it (e.g. skin tumors) or in a natural cavity (e.g. esophagus, uterus).

## Radiotherapy principles

DNA is the main target of ionizing radiation, whose major goal is to induce breaks in the double-helix of nuclear DNA. These breaks induce a cellular response (DNA damage response) that includes the activation of cell cycle checkpoints and repair mechanisms. In some cases, this response leads directly to cell apoptosis but, in most situations, cell death only occurs after the next attempt to enter mitosis, when damaged or deficiently repaired DNA will originate a mitotic catastrophe. This leads to irreversible loss of reproductive capacity and eventually to cell death [5]. Although ionizing radiation damages both normal and tumor cells, the aim of radiotherapy is to deliver the highest possible dose to the tumor, sparing as much as possible the surrounding normal tissues.

To make this possible, it is important not only to use advanced technology, but also to remember the 5 R's rule of thumb of radiobiology, that are crucial for treatment with conventional fractionation (1.8–2 Gray per fraction): *DNA Repair, Redistribution, Repopulation, Reoxygenation* and *Radiosensitivity*.

DNA repair is one of the main reasons for radiotherapy to be administered in multiple fractions, with curative daily treatments ranging from 3 to 8 weeks. Fractionation treatments allow for normal cells to *repair* sub-lethal damage induced by radiation. After the irradiation of a tumoral population, cells will be in different stages of the cell cycle. It is now clear that cells respond better to radiation in the G2 and M phases of mitosis. So, by dividing the treatment

into fractions we allow for tumor cells to *redistribute* their cellular clones to the most sensitive stages of the cell cycle.

In addition, fractionation of radiotherapy makes it possible for healthy cells to *repopulate* the space previously occupied by tumor cells. As the tumor mass decreases, *reoxygenation* of hypoxic tumoral zones is also permitted, making this radioinduced damage irreversible [6]. Besides these mechanisms, the *radiosensitivity* of the irradiated tissues will ultimately determine both the therapeutic response and the toxicity caused by the treatment [7], with the most radiosensitive cells/tissues being hematopoietic cells, germ cells, gastro-intestinal mucosa, skin and vascular endothelium [6].

Even with more advanced technologies, such as Intensity-Modulated Radiation Therapy (IMRT) or Volumetric-Modulated Arc Therapy (VMAT), Stereotactic Body Radiation Therapy (SBRT) and Image-Guided Radiation Therapy (IGRT) techniques, which potentially decrease the volume of healthy tissues included in the treatment field, the risk of early and late toxicity cannot be dismissed. Early toxicity occurs during treatment and up to 90 days after its completion, whereas late toxicity appears after that period, sometimes months or years after the treatment. The late effects of radiation are usually the dose limiting factor and tend to affect slowly proliferating tissues [8].

Factors that influence the incidence and severity of late complications are divided broadly into therapy-related or patient-related factors.

The main therapy-related risk factor is fractionation (dose per fraction). Hypofractionated schemes (delivering higher dose per fraction) have become increasingly common specially among low  $\alpha/\beta$  tumors such as breast and prostate cancer. Evidence from multiple phase 3 randomized control trials have shown similar tumor control rates and no increase in late toxicities [9–11]. Prostate cancer trials evaluating the role of moderate hypofractionation comparing to a conventional 2 Gy/fraction regimen have shown no differences in gastrointestinal and genitourinary late effects in both groups with only a small increase in risk of short-term gastrointestinal toxicities [9, 11]. These data form the backbone of the international consensus supporting the use of hypofractionation in prostate cancer [12] but evidence is still limited for late toxicities beyond 5 years posttreatment so it is crucial for the Radiation Oncologist to ensure the implementation of these treatments with proper technology and safety. As for breast cancer, three week hypofractionated regimens have shown to have similar rates of local recurrence, late normal tissue toxicity, and breast cosmesis at 10 years compared with conventional fractionation over 5 weeks [13, 14], so it is now standard treatment after breast conserving surgery [15].

Other risk factors for late toxicities include total dose delivered, total time of treatment, irradiated volume,

radiation technique and the combination with other treatment modalities (surgery or systemic therapy) [16].

Individual risk factors for late complications include patient age, smoking and drinking habits, anemia, collagen vascular diseases, infections or pre-existence of functional diseases or genetic conditions [17]. To explain late complications of radiotherapy two mechanisms have been proposed: the first includes the direct damage to the microvascular endothelium, due its fast cellular turnover, which results in an interruption of blood flow, a process denominated *endarteritis obliterans* (obliterative endarteritis) [18]. The other mechanism (fibrotrophic model) relates to the depletion of stem and parenchymal cells in the irradiated tissue, and its replacement by fibrotic tissue caused by the release of fibrogenic cytokines [19]. Both mechanisms can account for irradiated tissues becoming typically hypovascular, hypoxic and hypocellular.

### Hyperbaric medicine and radiation lesions

Hyperbaric Oxygen Therapy (HBOT) consists in the administration of oxygen in an inspired oxygen fraction close to one (100% oxygen), inside a hyperbaric chamber with a pressure 2 to 3 times higher than the atmospheric pressure at sea level (760 mmHg/1 ATA). This pressure increase will result in a very significant rise in blood and tissue oxygen pressure (close to 2000 mmHg and 400 mmHg, respectively). The oxygen content of arterial blood at 1 atmosphere absolute (ATA) is about 20 ml/dL but only 0.29 ml/dL corresponds to dissolved oxygen, the rest is bound to hemoglobin. By increasing the pressure up to 2 or 3 ATA there is an exponential increase in the amount of dissolved oxygen in the blood and tissues. Due to its diffusion capacity, dissolved oxygen crosses functional capillaries to the hypoperfused areas, allowing oxygenation of cells at risk, which will underpin most of the physiological and therapeutic effects of hyperbaric oxygen [20].

HBOT promotes mechanisms that trigger regeneration and healing as it enhances collagen production [21, 22], improves the function of osteoclasts and osteoblasts in bone remodeling [23], promotes angiogenesis and induces the release of stem cells from the bone marrow into the circulation, leading to the formation of new capillaries [24]. In addition, HBOT reduces radiation-induced damage by preventing the recruitment of neutrophils and macrophages [25, 26] and the imbalance of calcium homeostasis [27], by preventing the synthesis of cytokines, PGE<sub>2</sub>, Cox-2 [28], radioactive oxygen species [29], action of NO [30], IFN-gamma18 [31] and TNF-alpha [32]. Tissue swelling is probably improved through an osmotic effect of oxygen, while the establishment of a steep oxygen gradient across an irradiated tissue margin is a powerful stimulus to the growth of new blood vessels [23]. All these mechanisms support the

benefit of HBOT in the viability of irradiated tissues, playing an important role in the treatment of radiation lesions.

Irradiated tissues become hypovascular and hypoxic. With HBOT there is an improvement on neovascularization and oxygenation, promoting remodeling and improving the homeostasis, while diminishing inflammation.

### Background

Hemorrhagic cystitis typically presents between 6 months and 10 years after radiotherapy. It has a prevalence of 5–15% among patients irradiated in the pelvic area [33]. It manifests as haematuria, anemia, pollakiuria, dysuria, incontinence, or retention as a result of urethral obstruction by a clot. Multiple studies have demonstrated the significant effect hemorrhagic cystitis can have on patient-rated quality of life scales [34]. Different treatment methods may be considered: bladder instillation with specific agents, laser hemostasis through cystoscopy, specific arterial embolization and as a last resource cystectomy with urostomy [35]. Studies of intravesical agents used in the treatment of severe bladder hemorrhage show response rates higher than 50% [33]. HBOT is a non-invasive treatment that has become more prevalent in recent years, and studies have shown a complete response rate ranging from 27 to 100% of patients studied, with most showing more than 75% of patients with a complete response [36].

Radiation proctitis occurs as a late complication after pelvic radiotherapy. Its incidence was previously reported to be as high as 30%, but with recent advances in radiation techniques, it is estimated that only approximately 1–5% of patients treated for pelvic malignancies will experience symptoms related to late radiation effect [37]. It manifests as pain, diarrhea, fecal incontinence and rectorrhagia. Chronic radiation proctitis has a significant impact on patient's quality of life scores, causing devastating effects on psychological outcomes [38]. The therapeutic options include oral or rectal steroids, but the efficacy of corticosteroids alone has been poorly studied and anecdotal clinical experience with this approach has been disappointing [36]. Another option is the use of oral or rectal sucralfate, which may be used to decrease the bleeding associated with chronic radiation-induced proctitis, showing good response rates by 4 weeks [39]. Mesalazine or butyrate enema may also be used with some benefit in hastening recovery [40] and hemostatic control by endoscopy has shown to be effective in patients with mild and moderate radiation proctitis [36, 37, 41, 42].

Mandibular osteoradionecrosis develops years after radiotherapy for head and neck neoplasms. After the introduction of IMRT its incidence has been decreasing, being estimated at 5% [43]. It usually manifests after a local aggression (tooth extraction, trauma), with pain, trismus,

bone exposure, ulcer, fistula, abscess, xerostomia and dysphagia. Given the functional damage induced by mandibular osteoradionecrosis, quality of life is often severely affected [44]. In the literature, treatment includes antibiotic therapy and reconstructive surgery [45]. HBOT has been advocated in the prevention and treatment of osteoradionecrosis of the jaw after head and neck radiation therapy.

Radiation enteritis develops three or more months after radiotherapy. Late radiotoxic effects consist of a combination of submucosal fibrosis and vascular degeneration. Intestinal obliterating endarteritis causes ischemia, resulting in stenosis, fibrosis, or fistula formation, with increased intestinal permeability and bacterial growth. It is manifested by nausea, vomiting, abdominal pain, diarrhea, weight loss, malnutrition and melena. It is estimated that gastrointestinal symptoms have a negative impact in the quality of life of 50% of the patients submitted to pelvic radiotherapy. Additionally, 20–40% say that this effect is moderate or severe [46]. There are many therapeutic options, as dietary modification, antidiarrheal agents, antibiotics, bile acid sequestrants [47]. Surgical management is indicated in complicated and/or severe cases or in cases refractory to medical treatment [47]. One study showed high postoperative morbidity and need for parenteral nutrition after surgery [48].

When managing and treating late complications of radiotherapy, the above-referred therapeutic options are often of reduced effectiveness. HBOT, on the other hand, has an important role as a complementary treatment. HBOT has shown to be effective in reducing hematuria and its accompanying symptoms with total response rates of approximately 50% in the treatment of radiation cystitis [49]. As for radiation proctitis, there is evidence suggesting that HBOT significantly improves healing responses in patients with refractory toxicities, generating an absolute risk reduction of 32% [50]. HBOT has been used as a prevention before manipulation of irradiated bone or soft tissue (for example, dental extractions) in patients with mandibular osteoradionecrosis [49], although its benefit has been recently challenged with a randomized controlled trial showing no differences in late pain or quality of life [51]. Recent data from two randomized controlled trials accessing the effect of HBOT on mandibular osteonecrosis showed that HBOT was associated with an increased chance of healing independent of baseline ORN grade or smoking status as well as improved xerostomia, unstimulated whole salivary flow rate, and dysphagia compared to surgery alone. Despite these results, the statistically significant improvement was not observed due to insufficient recruitment [52].

There was a recognized need for an international scoring system for measuring and recording radiation morbidity. In 1995 the Late Effects Normal Tissues—Subjective, Objective, Management, Analytical (LENT-SOMA) scale was published. It was an attempt to produce a universal system

for measuring and recording the late effects of radiotherapy [53]. The published system incorporated four separate elements comprising subjective (a record of the patients' symptoms), objective (obtained by a clinician during a clinical examination), management (medical steps taken to ameliorate patients' symptoms), and analytical (an objective assessment of tissue effects) data [54]. The SOMA scales have been devised to monitor the response of all the individual organs or tissues known to be included in the target volume, and hence at risk of being damaged. For any treatment site a combination of different organ-specific scales would be selected. There are four degrees of injury within each category. The scores increase to reflect either the increasing intensity or frequency of the effect under observation, for example, increasing stool frequency [55]. An interesting point is that the scale takes into account the patient's point of view. It provides valuable data on the patient view and focus attention on symptoms that can be alleviated but may have not received sufficiently serious attention otherwise.

## Objectives

With this work we intend to present the results of treatment with HBOT of patients with radiation lesions in the Hyperbaric Medicine Unit (UMH) at Hospital Pedro Hispano (HPH) between October 2014 and August 2019.

Our main goal is to analyze if there is an improvement in the subjective parameter of the scale Late Effects of Normal Tissues—Subjective, Objective, Management, Analytical (LENT-SOMA) after HBOT.

## Materials and methods

All files of patients diagnosed with radiation lesions referred for Hyperbaric Oxygen Therapy (HBOT) at the HBOT Unit of Hospital Pedro Hispano between October 2014 and August 2019 were analyzed. Patients diagnosed with radiation cystitis, radiation proctitis, mandibular osteoradionecrosis and radiation enteritis, refractory to other treatments were included. During the defined period 112 patients were treated: 42 with radiation cystitis, 28 with radiation proctitis, 18 with mandibular osteoradionecrosis and 24 with radiation enteritis. Of these, 24 patients were lost to follow-up. The remaining 88 patients answered a questionnaire in the presence of a clinician to document the severity of symptoms before and after treatment with HBOT, using the subjective parameter of the scale Late Effects Normal Tissues—Subjective, Objective, Management, Analytical (LENT-SOMA)—Table 1.

**Table 1** Subjective evaluation of the LENT-SOMA scale

Parameter	Grade I	Grade II	Grade III	Grade IV
Subjective evaluation of the LENT-SOMA scale for radiation cystitis				
Haematuria	Occasional	Intermittent	Persistent with clots	Refractory
Dysuria	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Frequency	3–4 h intervals	2–3 h intervals	1–2 h intervals	Hourly
Incontinence	Weekly episodes	Daily episodes	2 pads / day	Refractory
Decreased stream	Occasionally weak	Intermittent	Persistent but incomplete obstruction	Complete obstruction
Subjective evaluation of the LENT-SOMA scale for radiation proctitis				
Tenesmus	Occasional urgency	Intermittent urgency	Persistent urgency	Refractory
Mucosal loss	Occasional	Intermittent	Persistent	Refractory
Sphincter control	Occasional	Intermittent	Persistent	Refractory
Stool frequency	2–4 per day	4–8 per day	> 8 per day	Uncontrolled diarrhea
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Subjective evaluation of the LENT-SOMA scale for mandibular osteoradionecrosis				
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory and excruciating
Mastication	–	Difficulty with solids	Difficulty with soft foods	–
Denture use	–	Loose denture	Inability to use dentures	–
Trismus	Present but unmeasurable	Preventing normal eating	Difficulty eating	Inadequate oral intake
Subjective evaluation of the LENT-SOMA scale for radiation enteritis				
Stool frequency	2–4 per day	4–8 per day	> 8 per day	Uncontrolled diarrhea
Stool consistency	Bulky	Loose	Mucous, dark, watery	–
Pain	Occasional and minimal	Intermittent and tolerable	Persistent and intense	Refractory /Rebound
Constipation	3–4 per week	2 per week	Once per week	No stool in 10 days

*LENT-SOMA* late effects of normal tissues-subjective, objective, management, analytical

Patients' demographics, primary location of the neoplasm, time interval between radiotherapy and the first symptoms and number of sessions of HBOT were reviewed.

HBOT treatments were performed in a 16-multi-place chamber with one daily session (Monday through Friday) at a pressure of 2.4 ATA for 90 min.

Using the SPSS Statistics program from IBM version 20, descriptive analysis of the data was performed. For continuous variables, after applying normality tests, the mean and standard deviation were found and *t* Student test of paired samples was applied for the subjective parameter of the LENT-SOMA scale before and after treatment with HBOT. Statistical significance was considered when  $p < 0.005$ .

## Results

### Radiation cystitis

Thirty-three patients were included in the study, of which 13 were women and 20 men, with a mean age of 69 years [45–82 years]. Regarding the primary location of the neoplasm that motivated treatment with radiotherapy, eight patients had cervical cancer, four endometrial carcinoma, 20 prostate cancer and one rectal carcinoma. The mean time

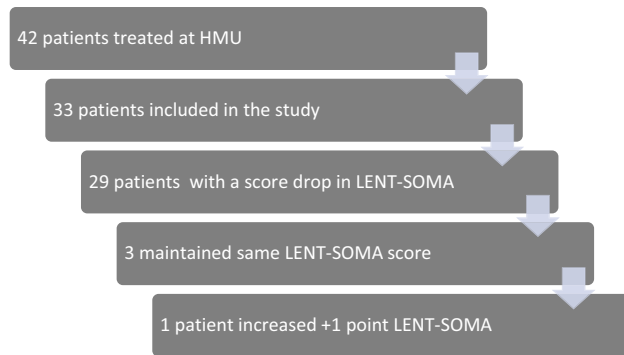
interval between radiotherapy and first episodes of haematuria was 62 [1–251 months]. The mean number of sessions was 42 [18–114 sessions].

Regarding the subjective parameter of the LENT-SOMA scale, there was an average decrease of 4 points  $\pm 2.6$  ( $p < 0.001$ ) after HBOT, with a mean score of  $9 \pm 3.3$  before HBOT and  $5 \pm 2.8$  after HBOT. In 29 patients an improvement (score drop) was observed, three patients maintained the same score and one patient worsened (despite improvement in hematuria, the frequency of urination per day has increased) (Fig. 1).

### Radiation proctitis

Twenty patients were included in the study, 10 women and 10 men, with a mean age of 65 years [35–81 years]. Regarding the primary location of the neoplasm that motivated treatment with radiotherapy, three patients had rectal carcinoma, seven cervical cancer and 10 prostate cancer. The mean time interval between radiotherapy and first symptoms was 36 [1–168 months]. The mean number of sessions was 55 [25–89 sessions].

When analyzing the subjective parameter of the LENT-SOMA scale, there was an average decrease of 2 points  $\pm 2.2$  ( $p < 0.001$ ) after HBOT, with an average score of  $7 \pm 3.2$



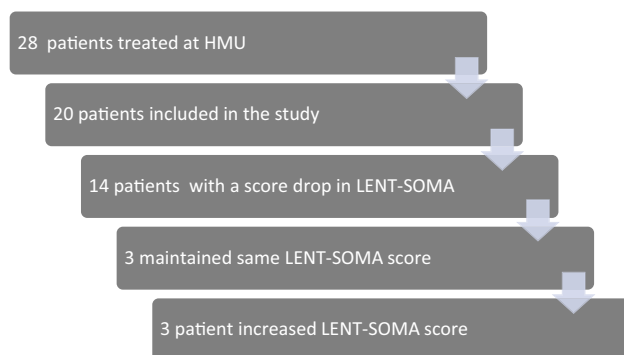
**Fig. 1** Results of patients with radiation cystitis treated at HMU. *LENT-SOMA* late effects of normal tissues-subjective, objective, management, analytical, HMU hyperbaric medicine unit

before HBOT and  $5 \pm 3.1$  after HBOT. In 14 patients an improvement (score drop) was observed, three patients maintained the same score and three worsened (one patient had resolution of pain but increased stool frequency and decreased sphincter control, another patient despite improvement in pain had worsening of mucosal loss, and a third patient experienced aggravated tenesmus and increased frequency of stools) (Fig. 2).

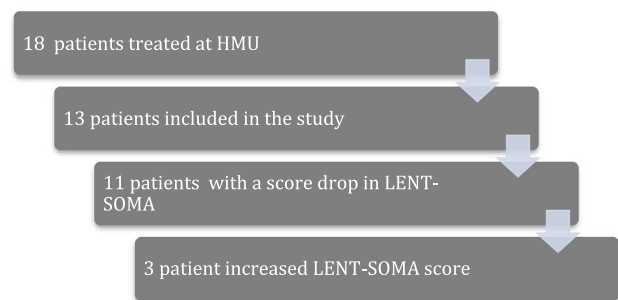
### Jaw/mandibular osteoradionecrosis

Thirteen patients were included in the study, 4 women and 9 men, with a mean age of 56 years [45–79 years]. Regarding the location of the neoplasm that motivated treatment with radiotherapy, nine patients had carcinoma of the oral cavity, two carcinoma of the nasopharynx and two carcinoma of the oropharynx. The mean time interval between radiotherapy and first symptoms was 36 [7–84 months]. The mean number of sessions was 57 [40–80 sessions].

Regarding the subjective parameter of the LENT-SOMA scale, there was an average decrease of 2.6 points  $\pm$  2.2



**Fig. 2** Results of patients with radiation proctitis treated at HMU. *LENT-SOMA* late effects of normal tissues-subjective, objective, management, analytical, HMU hyperbaric medicine unit



**Fig. 3** Results of patients with jaw/mandibular osteoradionecrosis treated at HMU. *LENT-SOMA* late effects of normal tissues-subjective, objective, management, analytical, HMU hyperbaric medicine unit

( $p < 0.001$ ) after HBOT, with an average score of  $5.7 \pm 2.9$  before HBOT and  $3.1 \pm 2.1$  after HBOT. In 11 patients an improvement (score drop) was observed, whereas two patients maintained the same score (Fig. 3).

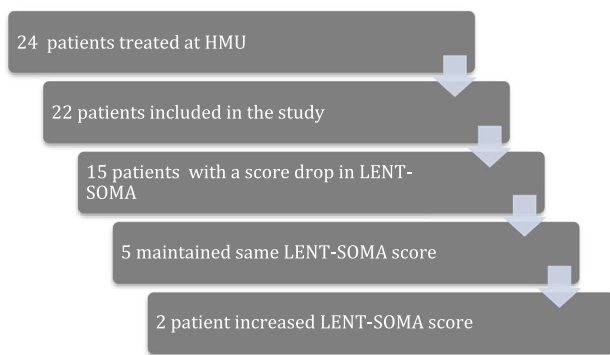
### Radiation enteritis

Twenty-two patients were included in the study, of which 16 were women and 6 men, with a mean age of 64 years [40–81 years]. Regarding the primary location of the neoplasm that motivated treatment with radiotherapy, nine had cervical cancer, seven rectal carcinoma, two prostate cancer, two retroperitoneal sarcoma, one gastric carcinoma, one colon carcinoma. The mean time interval between radiotherapy and first symptoms was 68 [5–168 months]. The mean number of sessions was 52 [18–70 sessions].

When analyzing the subjective parameter of the LENT-SOMA scale, there was an average decrease of 1.4 points  $\pm$  1.8 ( $p < 0.005$ ) after HBOT, with a mean score of  $6.5 \pm 3.6$  before HBOT and of  $5 \pm 2.0$  after HBOT. Fifteen patients had an improvement (score drop), five patients maintained the same score and two worsened (one patient had worsening constipation and one patient had worsening of pain) (Fig. 4).

### Discussion and conclusion

The multimodal approach of cancer patients has allowed for a significant increase in survival rates, with an inevitable increase in patients (long-survivors) who present side effects of the therapy performed. The use of advanced radiotherapy techniques allows for some dose-escalation approaches in the target volume while decreasing the dose in adjacent organs, which potentially reduces radiotherapy-related side effects. Late toxicities resulting from radiotherapy have a variable incidence but a known impact



**Fig. 4** Results of patients with radiation enteritis treated at HMU. *LENT-SOMA* late effects of normal tissues-subjective, objective, management, analytical, *HMU* hyperbaric medicine unit

on patients' quality of life. In the context of late lesions, Hyperbaric Oxygen Therapy appears as a complementary therapy to other therapeutic measures in the treatment of refractory radioinduced lesions. By increasing the pressure in the chamber to 2 or 3 absolute atmospheres (ATA) and inhaling 100% oxygen, there is an exponential increase in the amount of dissolved oxygen in the blood and tissues, allowing oxygenation of cells at risk. In addition to complementary symptomatic treatment, HBOT appears as the only treatment capable of promoting mechanisms that trigger tissue regeneration and healing.

According to the recommendations of the European Committee of Hyperbaric Medicine (ECHM), published in 2016, radiation cystitis, radiation proctitis and mandibular/jaw osteoradionecrosis are type 1 indications (with level of evidence B) for the performance of Hyperbaric Oxygen Therapy and radiation enteritis is an indication type 2 (with level of evidence B) [56].

The 2016 Cochrane review [23] included 14 trials on the use of HBOT to improve radio-induced lesions. There was some evidence of moderate quality that HBOT improved outcome in late radiation tissue injury affecting bone and soft tissues of the head and neck, for radiation proctitis and to prevent the development of osteoradionecrosis following tooth extraction in an irradiated field.

The data herein presented point to a significant improvement in the subjective parameters (reported by patients) of the various radiation lesions studied, and suggest that patients with late radiotherapy-related lesions could potentially benefit from treatment with Hyperbaric Oxygen Therapy. The present findings are consistent with previous trials [23] suggesting HBOT is an effective intervention for improving symptomatology in patients with radioinduced lesions. A recent study [57] documented an improvement in the LENT SOMA score of 3.7 in patients submitted to pelvic radiation, which is comparable with our results.

We acknowledge the existence of limitations in our study. The major limitation was the retrospective nature of its design accounting for the lack of detailed clinical information in several patients (radiation dose, previous treatments before referring to HBOT unit) as the patients were referred to our HBOT unit from other hospitals. Other limitations were the subjectivity of answers to the scale applied and the number of patients analyzed.

Notwithstanding these limitations, our results revealed a significant improvement in the clinical status of patients, which warrant further confirmatory studies.

**Acknowledgements** To all professionals who work in the Hyperbaric Medicine Unit of Hospital Pedro Hispano.

## Declarations

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Consent to participate** Not applicable.

**Consent for publication** The authors, jointly and severally, give the Publisher the permission to publish the work.

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