30-Year Experience of Treating Refractory Radiation-Induced HemorrhagicCystitis with Hyperbaric Oxygen Therapy: A Retrospective Single-CentreStudy

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Abstract

Introduction: Due to its considerable morbidity and mortality, radiation-induced hemorrhagic cystitis is an important complication of pelvic radiotherapy, with current conservative treatments having very limited effectiveness. Hyperbaric oxygen therapy is effective in the treatment of radiation-induced injuries, such as radiation-induced hemorrhagic cystitis. We aim to analyze the efficacy and safety profile of hyperbaric oxygen therapy in refractory hemorrhagic radical cystitis.

Methods: Retrospective analysis of the clinical records of 290 patients with refractory radiation-induced hemorrhagic cystitis treated with hyperbaric oxygen at our centre, between 1994 and 2022. The evolution of macroscopic hematuria was the parameter used to analyze the effectiveness of the treatment.

Results: In 14.8% of patients, other concomitant radiation-induced lesions were found, such as proctitis or enteritis. After an average of 37 sessions, 89.8% of patients had resolution of hematuria. Adverse effects were identified in 5.5% of patients. The need for blood transfusion and the time between radiotherapy and the appearance of macroscopic hematuria had a statistically significant correlation (value < 0.01) with the hematuria resolution rate.

Conclusion: Hyperbaric oxygen therapy was safe and effective inthe treatment of refractory radiation-induced hemorrhagic cystitis. The presence of concomitant radiation-induced injuries wasrelatively common, which makes hyperbaric oxygen an excellent choice as an initial therapy in these patients.

Keywords: Cystitis; Hematuria; Hyperbaric Oxygenation; Radiation Injuries; Radiotherapy/adverse effect.

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Introduction

Radiotherapy is one of the options to treat pelvic malignancies,particularly in the treatment of prostate cancer, cervical cancer, rectal cancer or urothelial carcinoma of the bladder. Despite themost recent technical developments, the development of collateral lesions in the surrounding tissues remains frequent, with its incidence ranging from 9.1% to 80%. With considerable morbidity and mortality, radiation-induced hemorrhagic cystitis is one ofthe most important adverse effects of irradiation of the pelvic region. Ionizing radiation impairs cell proliferation, causing progressive obliterating endarteritis and giving rise to hypocellular, hypovascular and hypoxic tissues, which leads to the development ofcystitis, with edema, ulceration, decreased tissue regenerationand fibrosis of the bladder mucosa.[1-4]

Radiation-induced cystitis can be classified as acute when it appears in the first three months after pelvic radiotherapy, with anestimated incidence of 50%, characterized by irritative symptoms, such as increased urinary urgency and frequency, dysuria, bladder spasms or hematuria (although hematuria is rare in the first three months after pelvic radiotherapy). There are validated scales that classify the severity of symptoms on a numerical scale of 1 to 5, according to the intensity of the symptoms and the impact on activities of daily living.[1,3,6] In the acute phase, radiationdirectly affects the cells of the urothelium, making the mucosamore susceptible to infections. These lesions promote the appearance of edema, hyperemia and inflammation of the mucosa. These acute phase changes are generally self-limiting,with the lesions disappearing or improving in the three to six weeks following radiotherapy.[2-4]

Chronic radiation-induced cystitis appears after three months of pelvic radiotherapy, and symptoms may appear several years after the end of pelvic radiotherapy. On average, according to data in the literature, the first symptoms of chronic radiation-induced cystitis appear two to three years after the end of radiotherapy, although cases of symptoms after more than twenty years have been described. The over all incidence is 5%-10%, and symptoms are quite variable, ranging from

intermittent mild symptoms to intractable macroscopic hematuria that is refractory to conservative treatment, requiring bladder catheterization, rinsing and transfusion support.[3,4]

The diagnosis of radiation-induced hemorrhagic cystitis isclinical, based on the anamnesis and clinical history, assessing the existence of pelvic radiotherapy in the past, and endoscopic, where hyperemic bladder mucosa, with the presence of telan giectasias and fragile mucosa, are frequently found. Macroscopic hematuria is a frequent finding, and may be intermittent, without hemodynamic repercussions, or frank and uncontrollable, requiring hospitalization, transfusion support, bladder irrigation andvisits to the operating room for bladder fulguration. As a last resort, emergency cystectomy may be the only life-saving option. Radiation-induced cystitis may ultimately result in death.[3,4] Although conservative techniques are currently recommended as first line therapy for hemorrhagic cystitis, their reduced long-term efficacy often means that more invasive techniques are needed to control hematuria.

By increasing tissue oxygenation, hyperbaric oxygen therapy promotes angiogenesis, leukocyte activity, fibroblast proliferationand collagen deposition, and is used to treat hypoxic and scarring lesions, increasing tissue regeneration. Although there has been increasing scientific evidence in favour of the use of hyperbaric oxygen as a treatment for hemorrhagic cystitis, there is a need for studies with a larger number of patients to assess its efficacy.[2,4]

At our centre, the first treatments with hyperbaric oxygen therapy began in 1994, with treatments having been carried out on more than 700 patients in its thirty years of existence.

At our centre, the severity of radiation-induced cystitis is assessed with the Portuguese Navy Radiation-induced Cystitis (PNRC) scale[5] a comprehensive classification that includes five different domains (hematuria, other lower urinary tract symptoms, functional compromise, endoscopic findings and the need for therapeutic intervention), each organized into six progressivelevels of severity.[5]

The purpose of this study was to evaluate the effectiveness ofhyperbaric oxygen therapy (HBOT) to treat refractory radiation-induced hemorrhagic cystitis.

Material and Methods

Population

We evaluated the clinical records of all patients with radiation-induced hemorrhagic cystitis refractory to conservative treatment who were treated with hyperbaric oxygen therapy at our centre between 1994 and 2022. The evolution of macroscopic hematuria at 12 months was the parameter used to analyze the effectiveness of the treatment.

Of the 780 patients treated at the center during the period, 15 (1.92%) were excluded because they were under 18 years of ageat the time of treatment, 26 (3.3%) abandoned treatment before completing the number of sessions initially prescribed, 449 had no data regarding the severity of hematuria or no data regarding the dose of radiotherapy administered (57.5%). Data from 290 (37.2%) patients treated at the center were analyzed and included in this study (Fig. 1).

Study Design

A 12-month time window was used to assess the resolution of hematuria. The rate of resolution of hematuria was also correlated with other categorical and continuous variables, namely sex, age, affected organ, ionizing radiation dose, time from the end of radiotherapy to the appearance of macroscopic hematuria and need for transfusion support. The existence of side effects caused by hyperbaric oxygen therapy was also analyzed as a tool to assess the safety of the treatment.

Inclusion Criteria

The inclusion criteria were age greater than or equal to 18 years, a known history of pelvic radiotherapy, a known history of radical cystitis documented by cystoscopy, with at least one episode of macroscopic hematuria and no previous HBOT. The exclusion criteria for treatment were the existence of contraindications, namely the

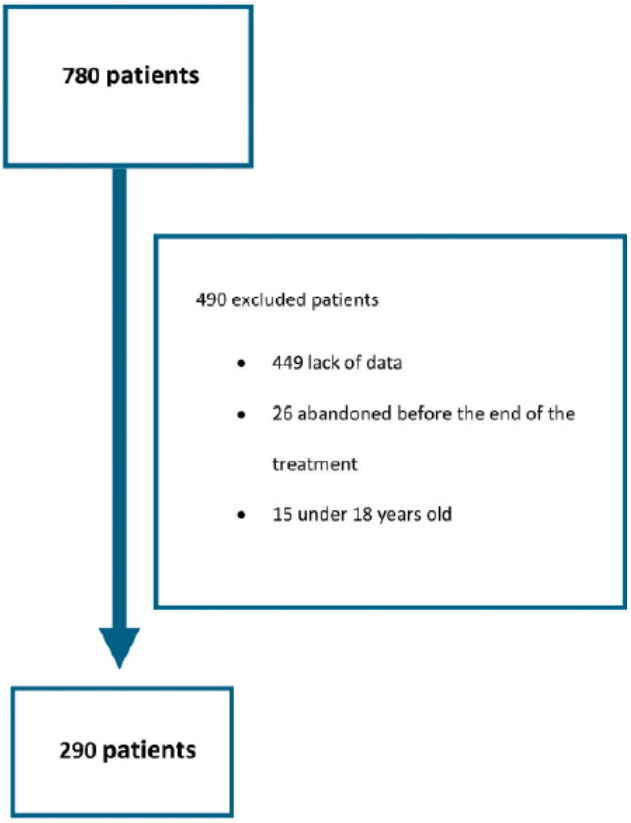


Figura 1 - Patient selection

existence of a diagnosis of epilepsy with seizures less than one year ago, or uncontrolled epilepsy, the existence of pneumothorax, the presence of subpleural bullae, severe claustrophobia, recent barotrauma and refusal or inability of the patient to sign the informed consent.

Statistical Analysis

The data obtained were processed in Microsoft Office Excel 2010 and analyzed in the software Statistical Package for Social Sciences (SPSS version 28.0 for Windows). Continuous variables were expressed as mean ± standard deviation. Categorical variables were presented as percentages. Statistical significance was assessed using the non-parametric Mann-Whitney test, defined as $p<0.01$.

Treatment

Patients were referred for treatment at the center from various urology departments in hospitals in mainland Portugal, after at least one conservative therapy had been proven to be ineffective. All patients treated at the center underwent a clinical assessmentin a Hyperbaric Medicine consultation at the center, to ensure that there were no contraindications for treatment.

After initial assessment and treatment decision, a set of 20 90 minute treatments of 100% oxygen at a pressure of 2.5 atmospheres (ATA) were prescribed in a multiplace chamber, once a day, five days a week (Fig. 2). After completion of the 20 sessions, the patients were reassessed by the center's medical team, who indicated whether to stop or maintain treatment, according to whether the hematuria resolved after the initial 20 sessions.

Results

Population Sample

Of the 290 patients studied, 52.0% were male (151 patients) and 47.9% were female (139 patients). The mean age of the patients was 67.39 years, ranging from 18 to 89 years. Patients with prostate cancer (47.5%) and cervical cancer (40.3%) constituted the majority of patients treated at the center with hemorrhagic cystitis. The total radiation dose ranged from 40 to 71 grays (Gy), with amean of 61.3.

Applying the PNRC scale, 70.6% of patients (205) had grade 2, 22.7% had grade 3 (66), 22.7% had grade 3 (66) and 6.5% (19) had grade 4. No patients were referred for treatment at the center with grade 5. In 91 patients (27.9%), hospitalization and transfusion support were required due to hemodynamic repercussions of hematuria. The mean time between hematuria and the start of treatment with hyperbaric oxygen therapy was 10.41 months.

After an average of 38.9 sessions, 86.2% of patients showed complete or partial resolution of hematuria, the latter defined as an improvement of at least one grade on the PNRC scale (complete resolution in 64.3% of patients). Adverse effects were identified in 5.5% of patients (16).

Assessmentof Hematuria Resolution Rate

During the 12-month follow-up, 64.1% of patients had complete resolution of hematuria (186 patients) and 86.2% of patients had improvement in symptoms, with a decrease in episodes of macroscopic hematuria, hospitalizations and need for transfusion support. When the PNRC scale was applied, 64.1% of patients (186) were classified as grade 1, 26.8% (78) as grade 2, 8.6% (25) as grade 3, and 0.3% (1) as grade 4. No patient was classified as grade 5.

Comparison between Population Subgroups

Several groups were also compared regarding the rate of resolution of hematuria. The need for transfusion support and the time between the end of radiotherapy and the onset of hematuria had a statistically significant correlation. In the subgroup that required transfusion support, 46.8% had complete resolution of hematuria, compared with 73.1% of the subgroup that did not receive transfusion support (*p* value 0.0019). Comparing

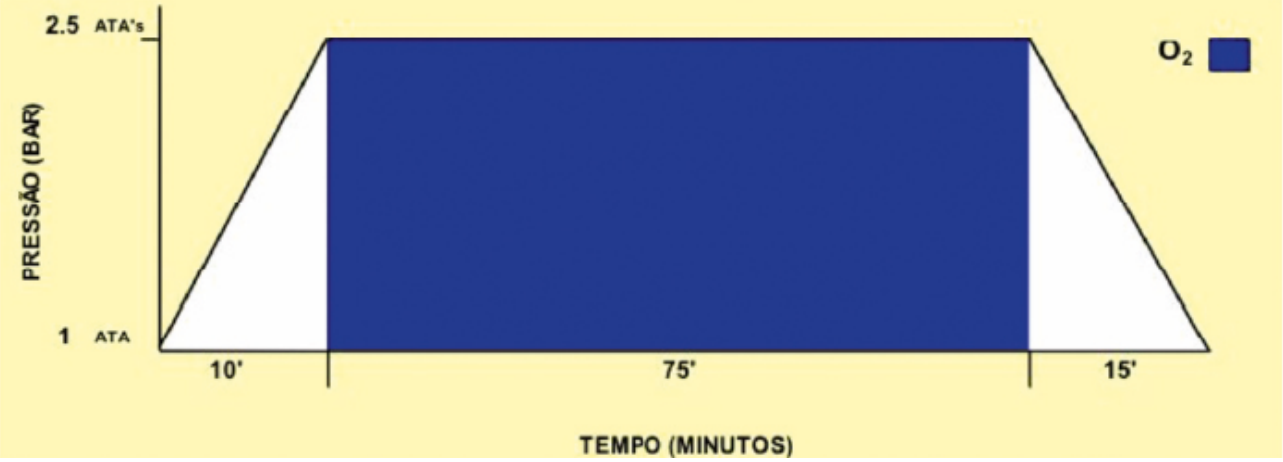


Figura 2 - HBOT Table at2.5 ATA

the time between the end of radiotherapy and the onset of hematuria, complete resolution was higher in the group whose hematuria appeared 60 months (5 years) or more after the end of radiotherapy (*p* value 0.0042). In the population whose hematuria appeared 60 months or more after the end of radiotherapy, 82% had complete resolution of hematuria at 12 months, compared with 60.2% ofthe group whose hematuria appeared less than 60 months afterthe onset of hematuria.

When comparing sex with the rate of resolution of hematuria, no statistically significant correlation was found. Age also did not reveal a statistically significant correlation with the resolution of hematuria when comparing populations aged 65 years or older and those aged less than 65 years. Comparing the populations with the most frequent cancers in the sample, prostate cancer and cervical cancer, the rate of resolution of hematuria did not have a statistically significant difference between the two samples. The dose of ionizing radiation administered also did not have a statistically significant difference between the population that received a dose less than or equal to 60 Gy and the population that received a dose greater than 60 Gy.

Tabela 1 - Sample characterization (qualitative variables).

SAMPLE CHARACTERIZATION (QUALITATIVE VARIABLES)	%(n)
SEX	
M	52.06 (151)
F	47.94 (139)
CANCER	
Prostate	47.58 (138)
Cervix?	40.34 (117)
Endometrium	5.86 (17)
Bladder	3.79 (11)
Rectum	1.03 (3)
Ewing's sarcoma	0.68 (2)
Ovary	0.34 (1)
Vulva	0.34 (1)

Tabela 2 - Sample characterization (qualitative variables), continuation.

AFFECTION OF MORE THAN ONE ORGAN	%(n)
Yes	14.83 (43)
No	85.17 (247)
TRANSFUSIONS	
Yes	31 , 37 (91)
No	6 8.62 (199)
SIDE EFFECTS	
Yes	5.51 (16)
No	94.48 (274)

Tabela 3 - Sample characterization (quantitative variables)

SAMPLE CHARACTERIZATION (QUALITATIVE VARIABLES)	Mean (min -máx) / Standard deviation
Age (years)	67.39 (1 8 -89)/ ±11.78
Total Radiations dose (GY)	61.3 (40-75)/ ±6
Radiotherapy-Hematuria time (months)	73.64 (0-324)/ ±84.48
Hematuria-OHB time (months)	10.41 (0-168)/ ±9
Radiotherapy-HBOT time (months)	84.05 (5-326)/ ±96
Number of OHB sessions	38.91 (7-179)/ ±21.81
Follow-up period (months)	12 (0-110)/ ±23.4

Tabela 4 - Response rates.

SAMPLE CHARACTERIZATION (QUALITATIVE VARIABLES)	Mean (min -máx) / Standard deviation
HEMATURIA	
Complete Resolution	64.13 (186)
Partial Resolution	22.06 (64)
Maintenance	5.51 (16)
Aggravation	8.27 (24)
HEMATURIA	
Resolved	86.21 (250)
Not Resolved	13.79 (40)

Tabela 5 - Classification (PNRC Scale) at first consultation andafter 12 months.

Classification (PNRC Scale)	1 consultation %(n)	12 months %(n)
1	0 (0)	64.13 (186)
2	70.68 (205)	26.89 (78)
3	22.75 (66)	8.62 (25)
4	6.55 (19)	0.34 (1)
5	0 (0)	0 (0)

Tabela 6 - Complete resolution rate by sex.

COMPLETE RESOLUTION RATE BY SEX	%	
M	60.47	*p* value 0.94
F	42.86	

Tabela 7 - Resolution rate for cancer.

COMPLETE RESOLUTION RATE BY CANCER	%	
Prostate cancer?	77.19	*p* value 0.97
Cervical cancer	64.47	

Tabela 8 - Resolution rate by age.

RESOLUTION RATE BY AGE	%	
>65 years	64.37	*p* value 0.32
<65 years old	69.23	

Tabela 9 - Time from radiotherapy to appearance of hematuria.

TIME FROM RADIOTHERAPY TO APPEARANCE OF HUMATURIA	%	
<60 months	60.3	*p* value 0.004
>60 months	82	

Tabela 10 - Radiation dose resolution rate.

RADIOTHERAPY DOSE RESOLUTION RATE	%	
>60 Gy	56.1	*p* value 0.24
<60 Gy	63.33	

Tabela 11 - Need for transfusion support.

NEED FOR TRANSFUSION SUPPORT	%	
Yes	46.8	*p* value 0.24
No	73.1	

Discussion

In this retrospective single-center study, hyperbaric oxygen therapy (HBOT) demonstrated a high rate of efficacy and afavorable safety profile in the treatment of refractory radiation-induced hemorrhagic cystitis. In a cohort of 290 patients treated over 30 years, complete resolution of hematuria was achieved in 64.1% of cases, while overall clinical improvement was observed in 86.2% of patients, confirming HBOT as a valuable therapeutic option in this challenging clinical setting. Most patients presented with moderate to severe disease at baseline, with more than one quarter requiring hospitalization and blood transfusion. This reflects the significant morbidity associated with radiation-induced hemorrhagic cystitis and emphasizes the need for effective second line therapies when conservative measures fail. The relatively low proportion of patients with the most severe stages maybe explained by logistical constraints related to the transfer ofcritically ill patients, despite the capability of the center to manage such cases. The outcomes observed in this study are consistent with previously published literature. Feldmeier *et al*

reported a hematuria resolution rate of approximately 76% in a systematic review of early studies, while Villeirs *et al* reported complete resolution rates of around 65% in a more recent systematic review.[8] Our findings, derived from one of the largest single-center cohorts published to date, further support the efficacy of HBOT in this indication. The need for blood transfusion emerged as a significant negative predictor of complete hematuria resolution. Patients requiring transfusion support had significantly lower response rates, suggesting that greater disease severity and more extensive radiation-induced vascular damage may reduce responsiveness to HBOT. In addition, a shorter interval between the end of radiotherapy and the onset of hematuria was associated with poorer outcomes. Early manifestation of hematuria may reflect more aggressive radiation injury to the bladder wall, leading to slower or incomplete tissue recovery, as previously described by Nakada *et al*.[9] No statistically significant associations were identified between treatment response and age, sex, primary malignancy, or total radiation dose. These findings suggest that the effectiveness of HBOT is largely independent of baseline demographic characteristics and cancer type, supporting it's broad applicability. HBOT was well tolerated, with adverse events occurring in only 5.5% of patients, mainly mild barotrauma and otalgia, all of which resolved with conservative measures. This low complication rate is consistent with, or lower than, rates reported in other published series,[7-11] reinforcing the safety of HBOT when performed in experienced centers. The main limitations of this study include its retrospective design and incompletedata for some variables, inherent to referral-based cohorts. Nevertheless, the large sample size, long observation period, and standardized treatment protocol strengthen the validity of the results. Overall, these findings support hyperbaric oxygen therapy as a safe and effective treatment for refractory radiation-induced hemorrhagic cystitis. Given its ability to promote tissue regeneration and address concomitant radiation-induced injuries, HBOT should be considered early in the therapeutic algorithm for patients with persistent or severe hematuria following pelvic radiotherapy.

Study Limitations

For some patients, it was not possible to obtain detailed information on the characterization of the primary cancer, the total radiation dose, the complementary diagnostic tests performed, and the therapies administered before the start of hyperbaric oxygen therapy, as well as the number of units transfused and the number and severity of each episode of macroscopic haematuria. This lack of data is the main limitation of our study and is because patients treated at our centre are referred from different centres throughout the country.

Conclusion

Hyperbaric oxygen therapy was safe and effective in the treatmentof radiation induced hemorrhagic cystitis. The presence of concomitant radiological lesions and the need for transfusion support were relatively common, which makes hyperbaric oxygen an excellent choice as initial therapy in these patients. The need for transfusion support and the time between the end of radiotherapy and the onset of hematuria had a statistically significant correlation with the rate of resolution of hematuria.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).

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Contributorship Statement

GB: Conceptualization, data curation, investigation, formal analysis, and writing the original draft.

TRO: Methodology, supervision, writing, reviewing and editing. DC: Data analysis, interpretation of data, writing, reviewing and editing.

CA: Supervision, project administration, and critical revision of the manuscript.

All authors read and approved the final version to be published.

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