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Review Article

Hyperbaric oxygen therapy for radiation cystitis after pelvic radiotherapy: Systematic review of the recent literature

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Abbreviations & Acronyms
CR = complete response
CTCAE = Common Terminology Criteria for Adverse Events
EPIC = Expanded Prostate Index Composite
HBO = hyperbaric oxygen
HBOT = hyperbaric oxygen therapy
LENT-SOMA = Late Effects Normal Tissue – Subjective, Objective, Management, Analysis score
NA = not available
PR = partial response
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RT = radiation therapy
RTOG I–IV = Radiation Therapy Oncology Group classification scheme for radiation toxicity, grade I–IV
SOMA = Subjective, Objective, Management, Analysis score

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Abstract: The present study assessed the efficacy of hyperbaric oxygen therapy in reducing symptoms of radiation cystitis, a specific type of iatrogenic injury to the bladder, by systematic review of recent literature. The MEDLINE, Embase and Web of Science databases were searched using combinations of the terms "radiation," "cystitis" and "hyperbaric oxygen" to identify articles evaluating patients with radiation cystitis, treated with hyperbaric oxygen therapy. Only recent (≤10 years) original studies were included. Data were extracted and pooled in order to calculate descriptive weighted averages. Articles were evaluated on their level of evidence. A total of 20 papers were obtained, resulting in a cohort of 815 patients who were treated with hyperbaric oxygen therapy for radiation cystitis. Overall and complete response rates varied from 64.8% to 100% and 20% to 100%, respectively. The weighted average overall and complete response rates were 87.3% and 65.3%, respectively. Adverse events were observed in 9.6% of the patients, but permanent side-effects were rare. The most prominent limitations were high cost and low availability. Hyperbaric oxygen therapy is effective in the treatment of radiation-induced cystitis, with minimal adverse events, but low availability and high cost. At present, evidence is low; therefore, more prospective studies are required.

Key words: bladder, hyperbaric oxygen therapy, iatrogenic injury, radiation cystitis, radiotherapy.

Introduction

Radiation cystitis is a specific type of iatrogenic injury to the bladder. It is a potential, but often intractable, complication of pelvic radiation therapy for treatment of pelvic malignancies (e.g. prostate, bladder, cervical, endometrial and rectal cancer). Although modern techniques in RT have enabled precise targeting of malignant tissue while maximally sparing the surrounding healthy tissues, acute (≤90 days after start of therapy) and late (>90 days) toxicity might still occur, primarily affecting the bladder (radiation cystitis). Radiation cystitis can be a complication of radiation doses starting from 45 to 55 Gy, and the risk increases significantly at cumulative doses of ≥60 Gy.[1]

Acute symptoms include urinary frequency, nocturia, dysuria and pelvic pain or discomfort, usually resolving spontaneously after 4–6 weeks. Late symptoms include pollakiuria (due to reduced bladder volume), urinary frequency, urgency, infections, retention and hematuria. They occur when acute symptoms have resolved, with a mean delay of 2 years after the last radiotherapy fraction.[2]

As radiation cystitis can seriously impact quality of life, adequate treatment is of utmost importance. Available options at present include bladder irrigation (with saline or specific solutions, such as alum, silver nitrate, formalin or hyaluronic acid), coagulation or selective embolization of bleeding vessels and HBOT.[2] However, these modalities are not always successful, and in severe intractable radiation cystitis, radical cystectomy is the only remaining option.[3]

In HBOT, 100% oxygen is administered in a highly pressurized chamber (usually ~2 atmospheres) for 5–7 days a week, for a daily duration of 60–90 min up to approximately 30–45 sessions. The aim of HBOT is to reverse the process of radiation-induced cellular hypoxia in

the bladder tissue through better diffusion of oxygen within the tissues. This is achieved through induction of neovascularization, and therefore angiogenesis and granulation tissue formation, fibroblast proliferation, and optimization of the cellular immune functions. Disadvantages of HBOT include claustrophobia during therapy, and logistic difficulties, as the patient needs to go to the center with pressurized chambers daily.[2–4]

There appears to be a large variation in techniques, treatment timing, length of follow up, symptom reporting and response rates in the published literature on HBOT for radiation-induced cystitis. Therefore, the purpose of the present study was to systematically review the recent literature to determine the role of HBOT in the reduction or resolution of symptoms of radiation-induced cystitis.

Methods

Studies were included if they fulfilled all the following requirements according to the PICOS criteria:[5] (i) Patients: men/women with radiation-induced cystitis; (ii) Intervention: treatment with HBOT; (iii) Control group: subjects receiving no HBOT; (iv) Outcome: reduction or resolution of symptoms related to radiation-induced cystitis; and (v) Study design: randomized controlled trials, cohort studies and case series, no case reports. Only original studies were included. The electronic MEDLINE (PubMed), Embase and Web of Science databases were searched for articles published within the past 10 years up to May 2018. Using MeSH vocabulary keywords and free texts, 113 articles were identified.

The articles were subsequently screened for eligibility through abstract and full text reading. Papers were excluded based on the following criteria: (i) review or absence of original data; (ii) case report; (iii) inclusion of other pathologies (e.g. radiation-induced proctitis) without separate subgroup analysis; and (iv) duplicated data from another included study.

A total of 68 articles were excluded through abstract reading. Another 25 papers were excluded by full text reading. Reference lists of the selected articles were subsequently reviewed to identify missed eligible articles, but no additional relevant papers could be obtained.

A detailed overview of the search and study selection according to the PRISMA guidelines is presented in Figure 1.

Data were extracted and pooled. If possible, patients who received chemotherapy as part of their cancer treatment were excluded from further analysis. Descriptive weighted averages were calculated, but no further statistical analysis was carried out due to lack of comparability across the studies.

The quality of the studies was evaluated using the Levels of Evidence for Therapeutic Studies, as defined by the Center for Evidence-Based Medicine.

Results

Patient population

The 20 retrieved studies resulted in a cohort of 815 patients, aged 15–91 years (Table 1). The indication for RT was prostate cancer in 58.9% of patients. Other indications were cervical, endometrial, bladder, anal, colorectal, ovarian, vaginal and vulvar cancer, Ewing's sarcoma, rectal alveolar rhabdomyosarcoma, and malignant lymphoma. Radiation doses ranged between 36 and 138 Gy to the pelvis. Of the 20 studies, 12 reported the interval between the final RT and the onset of symptoms, which ranged between 0 and 396 months.[1,6–16] Transfusion was carried out in the case of major blood loss, but just 11 studies reported the exact number of patients in whom blood transfusion was required.[6,7,9,11–14,16–19] A total of 13 studies reported inclusion of patients who had received other treatment modalities before HBOT.[1,6,9,10,12,14–18,20–22]

Quality of evidence

There was one non-blinded randomized trial, without a placebo group, showing a 2b level of evidence.[20] All other studies were level 4 (single-arm cohort studies, case–control studies without a control group and case series), of which three were prospective studies.

Treatment with HBOT

Details on HBOT

Hyperbaric oxygen was administered to all patients in a mono- or multiplace compression chamber, for 60–120 min, and with a pressure between 1.8 and 2.5 atmospheres (Table 2). The number of sessions ranged between one and 179 (mean or median cannot be reported due to inconsistency in data reporting). After completing HBOT, patients were followed for up to 19.2 years.

Outcome of HBOT

To evaluate the effect of HBOT on radiation cystitis, the results of the reviewed studies are divided into three categories: CR, PR and no response (Table 3). An exact definition of these categories according to the various studies is found in Table 3. In general, "complete response" indicates that the symptom is entirely absent after HBOT. "Partial response" means that the symptom persists, but is less severe than before treatment with HBOT. The "overall response rate" is the summation of the CR and PR. "No response" is used when the symptom does not show any improvement after therapy.

There are several different outcome measures that are used to describe the effect of HBOT on radiation cystitis. The most common of these is its effect on hematuria, which is discussed in nearly all included studies. Other parameters include the requirement of blood transfusion, aberrant findings on cystoscopy and pathology, dysuria, frequency, bladder irritability (assessed using modified Parson's questionnaires), pelvic pain, and the patient-perceived quality of life (EPIC questionnaire).[7,9] Frequency and pelvic pain were evaluated following the toxicity criteria for the bladder by the SOMA scale.[9]

Hematuria: A total of 12 studies used hematuria as the only parameter to describe the effect of HBOT in patients with

Table 1 Patient characteristics

Study	No. patients	Sex, *n* (%)		Mean age, years (range)	Primary tumor (%)	Mean total radiation dose, Gy (range)	Acute/late toxicity	Severity of toxicity	Transfusion required, *n* (%)	Therapy before HBOT, *n* (%)	Time from final RT to onset of hematuria, mean (range), months
		Male	Female								
Dellis *et al.*[13]	38	33	5	70.3 (56–82)	Prostate (73.7), bladder (18.4), rectum (2.6), cervix (5.3)	63.8 (32–80)	Both	Hemorrhagic cystitis (RTOG IV)	38 (100.0)	NA	21.4 (1–120)
Bouaziz *et al.*[11]	134	120	14	76 (32–90)	Prostate (NA), uterus (12.7), bone (NA), other	(55–73)	Both	Hemorrhagic cystitis (macroscopic hematuria, SOMA I-V)	37 (27.6)	NA	40 (1–396)
Lin *et al.*[1]	42	3	39	63 (42–82)	Cervix (92.9), bladder (7.1)	62.6 (50–90)	Late	Hemorrhagic cystitis	NA	42 (100.0)	118.8 (24–312)
Chong and Rice[22]	12	12	0	78 (66–85)	Prostate (75.0), bladder (25.0)	NA	Both	Hemorrhagic cystitis	NA	6 (50.0)	NA
Degener *et al.*[12]	12	10	2	72.9 (61–86)	Prostate (83.3), cervix (8.3), colon (8.3)	(60–78)	Both	Hemorrhagic cystitis (RTOG III–IV)	9 (75.0)	100.0	58.3 (5–234)
Mougin *et al.*[14]	71	63	8	72 (39–87)	Prostate (85.9), cervix (8.5), other	Median 66 (45–138)	Both	Hemorrhagic cystitis (CTCAE I-IV)	41 (57.7)	67 (94.4)	Median 38 (1–384)
Ribeiro de Oliveira *et al.*[6]	176	65 (36.9)	111 (63.1)	61.9 (18–85)	Cervix (50.1), prostate (31.8), endometrial (9.7), bladder (4.0), rectum (2.0), Ewing sarcoma (1.1), ovary (0.6), vulva (0.6)	56.3 (40–71)	Both	Hemorrhagic cystitis (macroscopic hematuria)	34 (19.3)	176 (100.0)	55.7 (0–313)
Tahir *et al.*[25]	20	NA	NA	NA	NA	NA	Late	Hemorrhagic cystitis	NA	NA	NA
Ferreira *et al.*[16]	70	32	38	Median 66.5 (34–91)	Cervix (48.6), prostate (42.9), anus (2.9), vagina (2.9), rectum (1.4), colon (1.4)	NA	Both	Cystitis (LENT-SOMA I-IV)	22 (31.4)	36 (51.4)	Median 27 (2–240)
Oscarsson *et al.*[7]	29	NA	NA	NA	Prostate (87.2), cervix (5.1), rectum (7.7)	NA	Both	Cystitis (EPIC ≤80)	0 (0.0)	NA	18 (0–120)

Study	No. patients	Sex, *n* (%)		Age (years)	Primary tumor (%)	Total radiation dose (Gy)	Acute/late toxicity	Severity of toxicity	Transfusion required, *n* (%)	Therapy before HBOT, *n* (%)	Mean time from final RT to onset of hematuria (months)
		Male	Female								
Liss *et al.*[8]	22	NA	NA	75.0 (54–87)	Prostate (100.0)	(66–78)	Late	Hemorrhagic cystitis (RTOG II–IV)	NA	NA	(12–204)
Shilo *et al.*[19]	32	22	10	Median 72.5 (48–88)	Prostate (65.6), rectum (3.1), endometrium (15.6), cervix (12.5), vagina (3.1)	NA	NA	Hemorrhagic cystitis (ASTRO 3–4)	15 (46.9)	NA	NA
Nakada *et al.*[9]	38	38 (100.0)	0 (0.0)	68.0 (49–82)	Prostate (100.0)	67.0 (46–96)	Late	Hemorrhagic cystitis (SOMA 2–5 for hematuria)	32 (84.0)	100.0	56.4 (23–120)
Oliai *et al.*[10]	11	NA	NA	67.0 (15–84)	Prostate (85.7), vulva (7.1), rectum (7.1)	(50–75.6)	Both	Hemorrhagic cystitis (mean LENT-SOMA 0.78)	NA	100.0	30.0 (5–324)
Vilar *et al.*[17]	38	21 (55.3)	17 (44.7)	66.5 (46–75)	NA	74.0 (64–106)	NA	Hemorrhagic cystitis (RTOG III–IV)	18 (47.3)	62.3	NA
Shao *et al.*[20]	20	NA	NA	60.0 (39–77)	Cervix (35.0), prostate (20.0), rectum (45.0)	(45–70)	NA	Hemorrhagic cystitis (macroscopic hematuria)	NA	15.0	NA
Parra *et al.*[15]	25	21	4	66.7 (42–80)	Prostate (80.0), cervix (12.0), endometrium (4.0)	NA	Both	Hemorrhagic cystitis	NA	100.0	31 (1–106)
Mohamad Al-Ali *et al.*[23]	10	7 (7.0)	3 (30.0)	79.5 (66–90)	Prostate (70.0), colon (10.0), cervix (10.0), vulva (10.0)	64.6 (50–70)	Late	Hemorrhagic cystitis (macroscopic hematuria)	NA	NA	NA
Yoshida *et al.*[18]	8	5 (62.5)	3 (37.5)	64.3 (47–73)	Prostate (50.0), cervix (25.0), lymphoma (12.5), bladder (12.5)	56.6 (42–70)	Late	Hemorrhagic cystitis (macroscopic hematuria)	3 (37.5)	50.0	NA
Safra *et al.*[21]	7	0 (0.0)	7 (100.0)	NA	NA	(50–71)	Late	Hemorrhagic cystitis (mean CTCAE 3.3)	NA	100.0	NA

Number of patients, patients' sex, age, primary tumor as indication for radiation therapy, total radiation dose, acute or late occurrence of radiation toxicity, severity of toxicity, need for blood transfusions, number and percentage of patients that underwent therapy other than HBOT before HBOT, and interval between the last radiation therapy session and the onset of hematuria in the individual studies.

Table 2 HBOT details

Study	No. sessions (*n*) Aim	Mean (range)	Pressure (atm)	Duration of one session, min (frequency)	Mean time to HBOT,† months (range)	Duration of follow up, months (range)
Dellis *et al.*[13]	Initially 30, maximum 45, cessation when CR	33 (20–78)	1.8	90, 5/week	5.4 (1–48)	29.3 (3–94)
Bouaziz *et al.*[11]	20–40 sessions	Median 50 (1–140)	2.5	2 90, 5/week	Median 19 (1–138)	12.0
Lin *et al.*[1]	NA	38 (10–87)	2.5	1 120, 5/week	NA	20.7 (3–49)
Chong and Rice[22]	30–40 sessions	NA	NA	90–120, 5/week	24 (12–60)	14.6 (1.9–49.7)
Degener *et al.*[12]	NA	38.5 (6–128)	2.4	3 30, 5/week	22.3 (0–110), median 11	68.6 (16–142)
Mougin *et al.*[14]	Initially 20 sessions	Median 29 (3–50)	2.5	2 90, NA	Median 8 (1–154)	NA
Ribeiro de Oliveira *et al.*[6]	Initially 20 sessions	36.5 (7–179)	2.5	90	13.7 (0–168)	12.0 (0–108)
Tahir *et al.*[26]‡	NA	NA	2.4	70	NA	NA
Ferreira *et al.*[16]	Initially 20 sessions	Median 40 (10–93)	2.4	80, 5/week	Median 8 (0–114)	Median 55.5 (4–85)
Oscarsson *et al.*[7]	Initially 30 sessions	(28–40)	2.4	90	NA	12.0
Liss *et al.*[8]	Initially 30 sessions	(30–60)	2.4	90	NA	26.4 (4–163)
Shilo *et al.*[19]	30 sessions	Median 30 (3–53)	2.0	90, 5/week	NA	Median 12 (5–74)
Nakada *et al.*[9]	As many as needed	62 (39–92)	2.0	90	(1–58)	136.2 (89–230)
Oliai *et al.*[10]	Initially 30 sessions	29.8 (10–40)	2.0	90–105	NA	39.0 (7–70)
Vilar *et al.*[17]	Initially 20 sessions	31.2 (20–48)	2.0–2.5	90	NA	36.3 (12–60)
Shao *et al.*[20]	30 sessions	NA	2.5	60	NA	18.0
Parra *et al.*[15]	40 sessions	Median 40 (15–44)	2.2	90, NA	4.7 (1–12)	21.2 (3–66)
Mohamad Al-Ali *et al.*[23]	As many as needed	NA	2.5	60	8.9 (3–34)	8.4 (12–72)
Yoshida *et al.*[18]	Initially 10 sessions	19 (10–42)	2.0	90	8.9 (3–34)	15.5 (2–31)
Safra *et al.*[21]	NA	27 (16–40)	2.0	90	NA	NA

†Mean duration of interval between onset of hematuria and initiation of HBOT. ‡As the study by Tahir *et al.* includes patients with multiple pathologies, no specific information was given regarding the radiation cystitis patients only.

hemorrhagic radiation cystitis.[6,8,11,12,14–19,23,24] Three other studies had separate results regarding the response to treatment of hematuria.[9,10,21]

The largest study included 176 patients.[6] The overall response percentage to HBOT was 89.8% (67.1% CR and 22.7% PR).

The second largest study included 134 patients, of whom 82.8% responded to HBOT 3 months after its initiation. Complete cessation of hematuria was seen in 41.7% of patients after 3 months.[11]

Mohamad Al-Ali *et al.* reported complete remission in two out of 10 patients treated with HBOT.[23] Interestingly, the control group, consisting of four patients that were not healthy enough to undergo HBOT, showed better results. It should be noted, however, that no distinction was made between patients with improved symptoms and patients with no improvement at all.

Summarizing all included studies, the overall response rate varied between 64.8% and 100.0% (86.4% weighted average across the studies) in studies that provided this overall response value.[6–18,20–22,25] The CR rate varied between 20.0% and 100.0% (63.6% weighted average).[1,6–8,10–23] HBOT did not yield any effect in up to 35.2% of patients.

Several influencing factors have been hypothesized to cause this wide range of overall response and CR rate to HBOT.

Ribeiro de Oliveira *et al.* showed that there was a significant correlation ($P = 0.026$) between the need for blood transfusion and persistence of hematuria.[6] However, in the absence of any multivariate regression analysis, causation could not be shown. Liss *et al.* showed that persistent hematuria after HBOT was more frequent in patients who had received more units of transfused blood (although no significant correlation was found, Mann–Whitney $P = 0.062$), and hematuria of lower RTOG stage was associated with increased resolution of hematuria after HBOT ($P = 0.023$).[8] Despite this negative correlation, Ribeiro de Oliveira *et al.* reported a total response to HBOT of 79.4% in transfused patients,[6] whereas Dellis *et al.* reported PR or CR in all patients in a population with RTOG grade IV radiation cystitis who all required blood transfusions.[13]

Bouaziz *et al.* and Mougin *et al.* showed that anticoagulant therapy was a significant negative predictive factor (OR 0.18, 95% CI not reported, $P = 0.002$ and OR 0.3, 95% CI 0.07–0.9, $P = 0.03$, respectively) for the successful therapeutic outcome of HBOT.[11,14] Ferreira *et al.* studied the negative predictive effect of other treatment modalities before HBOT, but found no significant correlation.[16]

Nakada *et al.* showed that the number of HBOT sessions was 25% lower in patients with a stable resolution of symptoms, than in patients with recurrent symptoms ($P < 0.001$).[9] In contrast, Ribeiro de Oliveira *et al.* (after post-hoc analysis and adjustment of significance levels for multiple comparisons) and Ferreira *et al.* could not identify a significant correlation between the number of sessions and treatment response.[6,16]

Another possible indicator for negative outcome is the interval between the completion of RT, onset of hematuria and start of HBOT. Nakada *et al.* reported that recurrent hematuria was more common in patients with a short interval between completion of RT and onset of hematuria

Table 3 Outcome of treatment with HBOT in the reviewed studies

Study	Study design	Timing of first results after conclusion of therapy	Clinical parameter(s)	Criteria for response	No. patients	Clinical response,% (*n*)				
						Total	Complete resolution	Partial resolution	No response, % (*n*)	Recurrence, % (*n*)†
Bouaziz *et al.*[11]	Retrospective	At 3 months after *initiation* of HBOT	Hematuria	Improvement of SOMA grade of hematuria	134	82.8 (111)	41.7 (56)	41.0 (55)	17.2 (23)	3.7 (5)
		At 12 months after *initiation* of HBOT			102	81.4 (83)	48.0 (49)	33.3 (34)	18.6 (19)	NA
Chong and Rice[22]	Retrospective	After follow up	Hematuria	Absence (CR) or reduction (PR) of macroscopic hematuria	12	66.7 (8)	50.0 (6)	16.7 (2)	33.3 (4)	NA
Mougin *et al.*[14]	Retrospective	Immediately	Hematuria	Absence (CR) or reduction of hematuria	71	64.8 (46)	52.1 (37)	12.7 (9)	35.2 (25)	26.8 (19)
Degener *et al.*[12]	Retrospective	Immediately	Hematuria	CR: RTOG 0 PR: improvement of RTOG grade	12	91.7 (11)	83.3 (10)	8.3 (1)	8.3 (1)	8.3 (1)
Ribeiro de Oliveira *et al.*[6]	Retrospective	Immediately	Hematuria	Absence (CR) or reduction (PR) of hematuria	176	89.8 (158)	67.0 (118)	22.7 (40)	10.2 (18)‡	13.6 (24)
Ferreira *et al.*[16]	Retrospective	After follow up	Hematuria	Absence (CR) or reduction (PR) of hematuria	70	91.4 (64)	71.4 (50)	20.0 (14)	8.6 (6)	NA
Liss *et al.*[8]	Retrospective	Over entire follow up	Hematuria	CR: absence of hematuria	22	NA	50.0 (11)	NA	NA	NA
Shilo *et al.*[19]	Retrospective	Immediately	Hematuria	CR: absence of hematuria	32	NA	84.4 (27)	NA	NA	40.7 (11)§
Vilar *et al.*[17]	Prospective	After follow up (12–60 months)	Hematuria	CR: absence of hematuria PR: residual non-anemic hematuria	37	100.0 (37)	97.3 (36)	2.7 (1)	0.0 (0)	0.0 (0)
Parra *et al.*[15]	Retrospective	Immediately	Hematuria	Absence (CR) or reduction (PR) of hematuria	25	96.0 (24)	96.0 (24)	4.0 (1)¶	0.0 (0)	0.0 (0)
Mohamad Al-Ali *et al.*[23]	Retrospective	Immediately	Hematuria	CR: absence of hematuria	10	NA	20.0 (2)	NA	NA	NA
Yoshida *et al.*[18]	Retrospective	Immediately	Hematuria	CR: absence of hematuria	8	75.0 (6)	75.0 (6)	NA	25.0 (2)	12.5 (1)
Nakada *et al.*[9]	Retrospective	2 years after conclusion of HBOT	Hematuria	Absence or improvement of symptoms	38	94.7 (36)	NA	NA	5.3 (2)	5.3 (2)
			RBC count in urine		38	92.1 (35)	NA	NA	7.9 (3)	2.6 (1)
			Blood transfusion		38	81.6 (31)	NA	NA	23.7 (7)	2.6 (1)
			Cystoscopic findings		38	89.5 (34)	NA	NA	10.5 (4)	5.3 (2)
			Urination pain		38	92.1 (35)	NA	NA	7.9 (3)	10.5 (4)
			Frequency		38	89.5 (34)	NA	NA	10.5 (4)	5.3 (2)
			Bladder irritability		38	94.7 (36)	NA	NA	5.3 (2)	7.9 (3)

†Recurrence after initial results, during or after follow up. ‡In two patients, symptoms aggravated, and in 16, the status remained stable. §Recurrence as the percentage of the CR group. ¶One patient was treated with laser coagulation of bleeding vessels due to acute hemorrhage, during the HBO treatment, and was therefore categorized as non-responsive.

(2.0 ± 9.0 years *vs* 4.0 ± 1.6 years, $P < 0.001$), and with a long interval between the onset of hematuria and initiation of HBOT (2.3 ± 1.2 years *vs* 0.7 ± 0.5 years, $P < 0.001$). It was reported that in the non-recurrent cases, the latter interval was 0.7 years on average (SD 0.5 years, range 0.1–1.8 years), whereas it lasted 2.3 years (SD 1.2 years, range 0.2–4.8 years) in the recurrent cases.[9] This was corroborated by Dellis *et al.*, who observed that all patients with a CR had their HBOT within a mean period of 4.9 months (range 1–6 months) after the onset of hematuria, whereas this interval was significantly longer (22 months, range 8–48 months, $P < 0.001$) in patients with a PR.[13] Ferreira *et al.* also showed a significant correlation ($P < 0.05$) between the resolution of hematuria and a shorter interval between the onset of hematuria and initiation of HBOT, but not between the resolution of hematuria and a shorter interval between termination of RT and onset of haematuria.[16] This correlation was not significant in two other studies.[6,12]

Nakada *et al*. did find a significant correlation between higher radiation dose and recurrent hematuria (62 Gy *vs* 76 Gy, $P < 0.001$). Patients with sustained remission of symptoms had received an 18% lower radiation dose than patients with recurring symptoms.[9] Comparison of the mean age in the recurrent and non-recurrent group did not yield a statistically significant correlation.[9] Ribeiro de Oliveira *et al.* and Ferreira *et al*. could not confirm any correlation between both age and radiation dose and resolution of hematuria due to HBOT.[6,16]

Other clinical parameters: Besides hematuria, seven studies used additional clinical parameters related to radiation cystitis to evaluate the effect of HBOT. Lin *et al*. reported that 90.5% of the included patients had an improvement in cystitis-related symptoms, including hematuria, urgency and/or frequency.[1] It should be mentioned that not all patients suffered from hemorrhagic cystitis in the study by Lin *et al*.

Dellis *et al*. described a clinical response as cessation or improvement of hematuria, no more need for transfusion and improvement of endoscopic or histopathological findings in the bladder mucosa.[13] Complete disappearance of these symptoms was reported in 86.8% of the patients. All patients showed a decrease of at least one RTOG grade.

Tahir *et al*. evaluated HBOT in patients with radiation-induced toxicity of the head and neck region (e.g. xerostomia and osteoradionecrosis of the mandible), pelvis (primarily radiation proctitis and cystitis) and other sites (e.g. breast pain, chest wall fibrosis), with separate subgroup analysis. They showed that 85.0% (17/20) of patients with radiation-induced hemorrhagic cystitis had improvement of symptoms (the exact symptoms were not specified), among whom 30.0% showed a major response (improvement of CTCAE grade by ≥2) and 55.0% a minor response (improvement of CTCAE grade by 1).[25] As a major response did not necessarily mean complete resolution of symptoms, and a minor response could lead to a complete resolution of symptoms in patients with only low-grade cystitis, data of the study by Tahir *et al.* could not be categorized as CR or PR in Table 3, and were hence shown as "NA."

Shao *et al*. examined the effect of HBOT on hematuria, as well as other cystitis-like symptoms, such as frequency, dysuria and pelvic pain. They reported a CR in 75.0% of patients after a 30-session treatment.[20] Just 5.0% of patients had no clinical response at all.

Nakada *et al.* assessed several radiation cystitis-related symptoms, including hematuria, RBC count in urine sediment, required number of blood transfusions, cystoscopic findings, micturition pain, frequency and bladder irritability.[9] For all these parameters, a significant improvement was observed, with at least some improvement in 81.6% of patients.

Oliai *et al*. reported an improvement of the LENT-SOMA score in all patients, from 0.78 pre-HBOT to 0.20 post-HBOT.[10] This score incorporates the patients' subjective and objective symptoms, along with the management of the disease and objective assessment of tissue effects.

Safra *et al.* assessed hematuria and dysuria.[21] All of the included patients had a complete resolution of hematuria, and 85.7% had a complete disappearance of dysuria.

Patient-perceived quality of life: Oscarsson *et al*. studied the patients' subjective perception of symptoms, using EPIC questionnaires.[7] A good quality of life was defined in that study as an EPIC score of ≥80. After treatment with HBOT, 31.0% of the patients reached this score, whereas they all had a score of <80 before HBOT. Another 44.8% showed an improvement of the EPIC score, yet remained with symptoms, significantly affecting patients' quality of life.

Summary: Any improvement of various cystitis-related symptoms was observed in 64.8–100% of the patients, with a weighted average of 87.3%. The majority of the patients (weighted average 65.3%, range 20.0–100.0%) were free of symptoms after HBOT. Only in up to 35.2% of patients, no improvement was observed.

Follow up and recurrence of symptoms

Studies with a longer follow-up period tended to show a recurrence of symptoms after the initial positive response to HBOT in some patients. In studies that provided recurrence rates, the mean follow-up period ranged from 12.0 to 136.2 months, with recurrence rates ranging from 0.0 to 40.7% (Tables 2,3).[6,9–15,17–19]

The longest follow-up period was reported by Nakada *et al*., with 32 patients still available for evaluation.[9] After 2 years of follow up, 95% of patients were free from hematuria, but this proportion decreased to 83% after 7 years and 81% at 11.6 years. Similar trends were observed for other symptoms (in decreasing order: red blood cell count in urine, urinary frequency, pain on urination and cystoscopic abnormalities). That study also allowed separating CR from PR and non-responses at 11.6 years, showing that the majority of patients still had a CR, notwithstanding a gradual decrease over time.

Adverse events

Adverse events due to increased pressure in the ear occurred in up to 33.3% of patients (Table 4). It is of note that this

Table 4 Adverse events occurring in patients treated with HBOT

Study	Patients with adverse events, % (*n*)	Adverse event, % (*n*)
Dellis *et al.*[13]	NA	NA
Bouaziz *et al.*[11]	15.7 (21)	Barotraumatic otitis 14.2 (19) Convulsions 0.7 (1) Respiratory decompensation 0.7 (1)
Lin *et al.*[1]	0.0 (0)	0.0 (0)
Chong *et al.*[24]	NA	NA
Mougin *et al.*[14]	22.5 (16)	Barotraumatic otitis media 12.7 (9) Vision disorder 7.0 (5) Finger paresthesia 1.4 (1) Pain during mobilization 1.4 (1)
Degener *et al.*[12]	0.0 (0)	0.0 (0)
Ribeiro de Oliveira *et al.*[6]	1.7 (3)	Ear barotrauma 1.7 (3)
Tahir *et al.*[25]	15.2 (12/79†)	Ear barotrauma 10.1 (8/79†) Eye barotrauma 3.8 (3) Dental pain 1.7 (1)
Ferreira *et al.*[16]	4.3 (3)	Barotraumatic otitis 4.3 (3)
Oscarsson *et al.*[7]	NA‡	NA‡
Liss *et al.*[8]	NA	NA
Shilo *et al.*[19]	18.8 (6)	Eardrum perforation 12.5 (4) Mild hemoptysis 3.1 (1) Vertigo 3.1 (1)
Nakada *et al.*[9]	NA§	NA§
Oliai *et al.*[10]	33.3 (5/15‡)	Otalgia 33.3 (5/15‡)
Vilar *et al.*[17]	2.6 (1)	Ear barotrauma 2.6 (1)
Shao *et al.*[20]	NA	NA
Parra *et al.*[15]	8.0 (2)	Barotraumatic otitis 8.0 (2)
Mohamad Al-Ali *et al.*[23]	0.0 (0)	0.0 (0)
Yoshida *et al.*[18]	0.0 (0)	0.0 (0)
Safra *et al.*[21]	0.0 (0)	0.0 (0)

†A subgroup analysis of only patients with radiation cystitis was not available; therefore, the results of the total population of patients with pelvic toxicity in the studies by Tahir *et al.* and Oliai *et al.* are shown in this table. ‡No major events were recorded, but minor events were not assessed in the study by Oscarsson *et al.* §Otalgia did occur in some patients in the study by Nakada *et al.*, but their number was not available.

also included a simple otalgia (33.3% of patients in the study by Oliai *et al*. experienced otalgia without further damage[10]), and severe or permanent damage to the ear was rare. Eye problems, such as vision disorders, occurred in up to 7.0% of patients. Other side-effects, such as finger paresthesia, convulsions, respiratory decompensation, dental pain, hemoptysis and vertigo, were reported, but only in a minority of the patients.

The pooled adverse event rate of all reviewed studies was 9.6% (range 0–33.3%).

Discussion

Based on the present review, an overall positive effect of HBOT is suggested, with a weighted average CR rate of 65.3% across the studies. HBOT did not yield any effect in up to just 35.2% of patients. In 64.8–100.0% of patients (weighted average 87.3%), any response to the treatment was observed.

A few factors that might be associated with lower efficacy of HBOT in the treatment of radiation cystitis (more specifically hematuria) have been described, although the correlation between these factors and suboptimal results or treatment failure is not consistently significant.

One of the parameters in the evaluation of hematuria is the need for blood transfusions before HBOT, as the most severe cases of hemorrhagic radiation cystitis cause the most blood loss and hence require more blood transfusions. However, it is of note that the need for transfusion therapy is not a contraindication for HBOT, as response rates to HBOT remain high.[6,13]

Other treatment modalities before HBOT (such as instillations with chemical agents, embolization, coagulation etc.) might influence the response rate of HBOT: such patients are likely to have more severe hemorrhagic cystitis, as they did not respond to these other therapies. Furthermore, earlier treatments might have caused additional injury to the bladder tissue, possibly inducing a condition in which the radiation cystitis is more refractory to treatment.[24,26]

Other parameters are the patient's use of anticoagulant therapy (as these patients are more prone to any sort of bleeding) and the number of delivered HBOT sessions, as the more HBOT sessions a patient requires, the more resistant their disease might be.

Some authors also stressed the importance of the interval between the completion of RT, onset of hematuria and start of HBOT. A possible explanation for the negative effect of a long interval between onset of hematuria and start of HBOT is that HBOT administered early in the process of radiation cystitis is likely to be more effective in regenerating tissue, and hence breaking the vicious circle of bladder tissue damage resulting from chronic hypoxia.[24] In addition, the negative effect of a short interval between completion of RT and the onset of hematuria might be the consequence of a higher severity of radiation cystitis after delivery of higher radiation doses.[27] As mentioned earlier, higher radiation doses might be responsible for a higher severity of radiation cystitis. The resulting hematuria thus presents earlier in the disease process and is more difficult to resolve with HBOT.

Mohamad Al-Ali *et al*. mentioned that the patient's age might be associated with lower efficacy of HBOT.[23] However, no statistically significant correlation between patient's age and less favorable outcome of HBOT were reported in the included studies. Chong *et al*. reported a better outcome of HBOT in younger patients, but stressed that this finding was inconclusive due to probable confounding factors, such as diabetes mellitus, cigarette smoking, atherosclerosis or vascular insufficiency, which are more common in elderly patients.[22]

Some variations are undoubtedly caused by the paucity or inadequacy of data. For example, the CR rate in the study by Mohamad Al-Ali *et al*. was remarkably low.[23] This is probably partly due to the fact that just 10 patients were included, and one of the patients did not complete all 30 sessions of HBOT due to intolerance. No further information on this

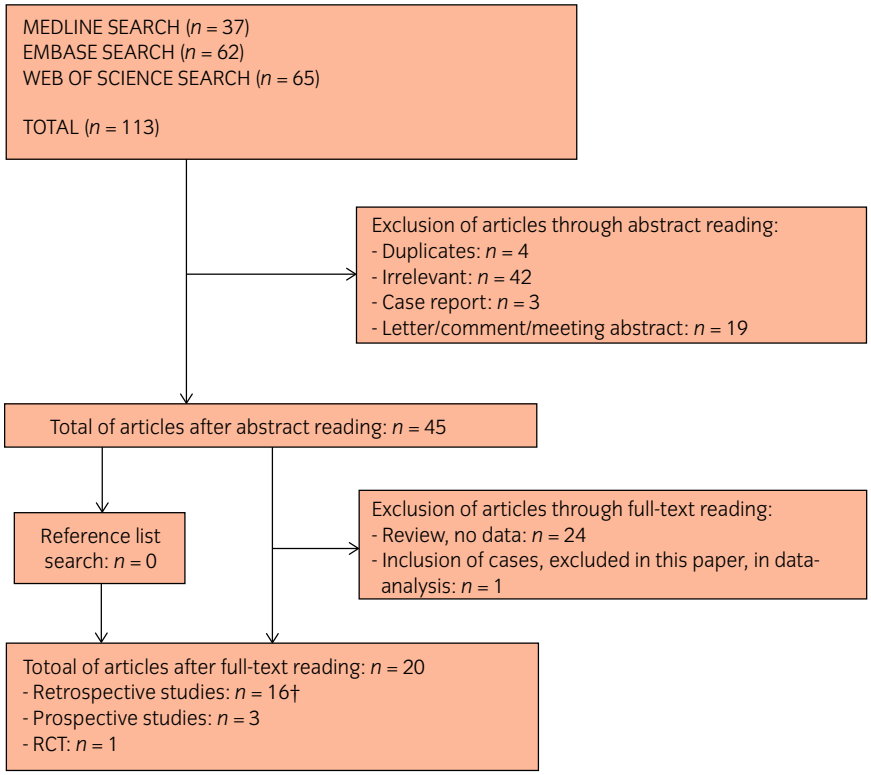

Fig. 1 Study selection process in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[28] The MEDLINE, Embase and Web of Science databases were searched using combinations of the terms "radiation cystitis," "radiation therapy" and "HBOT." After abstract reading, 45 potential articles were evaluated by full-text reading, after which 20 articles were selected for analysis. †Studies with prospective inclusion, but retrospective analysis, were categorized as retrospective (Bouaziz *et al.*). RCT, randomized controlled trial.

patient was provided, neither was this patient excluded from further analysis. Furthermore, in the group of patients without CR, no distinction was made between those with improvement of hematuria and those without any clinical response.

A final reason for varying success rates of HBOT in the treatment of hemorrhagic radiation cystitis is that there was huge heterogeneity between the studies with regard to populations, treatment schedules, outcome measures assessed and methods to assess these outcomes. Several authors used different definitions for their response assessment; for example, the absence or reduction of hematuria, improvement of CTCAE grade and so on. Furthermore, patient populations were diverse (regarding age, radiation dose received, severity of toxicity and so on), as were the study methods in the reviewed studies. This is most likely the most important reason why several of the abovementioned parameters, although relevant in the individual studies, do not seem to be sufficient as an explanation for the different outcomes across the studies.

In the studies with a longer follow-up period, up to 40.7% of the patients that initially responded to the treatment tended to show a recurrence of symptoms.[6,9–15,17–19] These recurrent cases seem to be the more severe cases of radiation cystitis, as Nakada *et al.* found significant correlations between the recurrent cases and a higher radiation dose, higher number of HBO treatments, a shorter interval between conclusion of RT and onset of hematuria, and a longer period of time between onset of hematuria and onset of HBOT.[9] Nevertheless, the majority of the patients included in that study, still had a CR at the end of the follow-up period. Furthermore, although the recurrence rate was higher in patients with negative prognostic factors (e.g. higher radiation dose, blood transfusion etc.), than in other patients, good response rates were still achieved in these former patients, as was shown by Ribeiro de Oliveira *et al.*[6]

In the case of recurrence of symptoms, administering additional sessions of HBOT is an option. Mougin *et al.* and Oliai *et al.* reported that a second course of HBOT was administered to 47.4% and 25.0% (one patient) of the recurrent patients, respectively, which proved effective in 88.9% and 100% of these patients, respectively.[10,14] Yoshida *et al.* reported that one patient with recurrence of hematuria was retreated with HBOT for every recurrence until there was complete resolution of hematuria.[18]

None of the other included studies provided specific results regarding retreatment with HBOT; therefore, no conclusions can be drawn as to whether or not retreatment is effective.

Finally, although 11 studies reported the recurrence rate, no further investigation was carried out on potential risk factors for recurrence.[6,9–15,17–19] This is most probably due to the small sample size of all of these studies or the short mean follow-up period.

HBOT seems to be effective in treating radiation cystitis, but as it requires the patient to spend quite some time in a high-pressure environment, potential adverse events might offset the positive effects of HBOT. Problems with pressure equalization seem to be the most frequent adverse event. In the included studies, however, dental pain (due to sinus barotrauma) and vision disorder (due to eye barotrauma) were exceedingly rare, whereas otalgia (due to ear barotrauma) was more frequently reported in the included studies, and in one study even affected one-third of the patients.[10] It is of note that the majority of these cases include fully reversible ear barotrauma, in up to just 5% requiring myringotomy.[25]

Overall, HBOT can therefore be considered as an effective and safe treatment.

The availability and cost-effectiveness of high-pressure oxygen tanks is a critical factor in the success of HBOT. For standard HBOT, patients are expected to attend daily sessions of 60–90 min, 5–7 days a week at a limited number of locations where HBOT is provided. Limited availability in certain areas, together with the duration of treatment, might eventually preclude the widespread use of HBOT.

Furthermore, HBOT is not inexpensive. For example, Degener *et al*. estimated the cost of one HBOT session in Germany in 2015 at €200,[12] whereas Ferreira *et al*. reported a mean cost of €134 per session.[16] The cost of HBOT varies from country to country, as does the reimbursement by the national healthcare systems. The factual cost to the patient or to society cannot be commented on here, as this is beyond the scope of our review. However, given the fact that usually approximately 20–30 sessions are applied as initial treatment and more as deemed necessary, treatment with HBO can be quite expensive. This must be balanced against the costs and benefits of other, potentially less expensive and less time-consuming options. However, in patients with radiation cystitis refractory to these other conservative options, HBOT is still a valuable, non-invasive treatment strategy to be considered before selective embolization or cystectomy are carried out.

Another limitation to the application of HBOT in the standard care of radiation cystitis is the lack of high-quality studies on its effectiveness. Apart from the randomized trial by Shao *et al*. (evidence level 2b), all of the studies included in this systematic review are level 4. Furthermore, just three of the included papers report on prospective studies, whereas a systematic review ideally includes only prospective randomized controlled trials. Therefore, new high-quality studies are necessary to determine whether HBOT should have a place in the standard care of radiation cystitis.

Hyperbaric oxygen therapy is a safe and effective treatment for radiation cystitis, but its availability is limited and the cost is high, so the question is raised as to whether HBOT should be used as a first-line treatment modality (before any other therapeutic option) or rather a last resort treatment modality (when everything else has failed).

Studies advocating early administration of HBOT stress the assumed higher effectiveness of HBOT when administered early after onset of hematuria. Chong *et al*, for instance, showed significantly higher therapeutic response rates in patients who had received HBOT within 6 months after onset of hematuria ($P = 0.003$).[24] This was corroborated by Nakada *et al*. and Dellis *et al*, who both reported less recurrences in the case of early administration of HBOT.[4,9] Chong *et al*. postulated that this observation was due to the fact that early intervention with HBOT might enhance tissue regeneration, and prevent chronic sloughing and scarring of hypoxic bladder tissue.[24]

Furthermore, treatment with HBOT does not cause damage to the bladder tissue, as might be the case with other treatment modalities; for example, cystoscopic coagulation or instillations with chemical agents. HBOT is the only treatment modality that even promotes tissue healing and angiogenesis.[24] In the case of treatment failure, no additional damage will have been induced, and other treatment modalities can still be attempted.

Finally, HBOT is also a valuable systemic treatment option. This is particularly interesting in patients with other radiation-induced toxicities (e.g. proctitis, scar complications etc.), as HBOT might improve or resolve multiple toxicities immediately, with no need for a combination of several individual treatments.[6,21]

However, there are also good arguments for keeping HBOT as a last resort. The first and most important of these is the fact that HBOT has also been proven to be effective after several other conservative therapies. In the study by Ribeiro de Oliveira *et al.*, all patients received one or more conservative treatment modalities, yet a CR rate of 67.0% was achieved.[6] Although hematuria reoccurred in some of the patients (13.6%), more than half of the patients were free of hematuria (that was refractory to other treatment) after treatment with HBOT. Also in Nakada's long-term follow-up study, all patients had previously undergone conservative treatment.[9] At 11 years after conclusion of HBOT, 71.8% of the patients were free of hematuria.

Second, there is no evidence that HBOT is more effective as a first-line treatment modality than other conservative treatment modalities. On the contrary, a randomized trial by Shao *et al*. compared 20 patients receiving HBOT with 16 patients receiving hyaluronic acid instillation, and the treatment outcome was very similar in both groups, although that study was possibly underpowered to show a significant difference.[20] There are no other comparative trials at present, so more studies on this matter are necessary. For now, the fact that there seems to be no superiority in the effectiveness of early HBOT might discourage the use of HBOT as a first-line treatment.

Finally, as mentioned earlier, treatment with HBOT is expensive and very time-consuming. This might limit generalized first-line use of HBOT for every patient with radiocystitis.

HBOT is effective in the treatment of hematuria and other symptoms related to radiation cystitis, although the effect might decrease with time. Factors that could be associated with suboptimal outcome or failure of HBOT include the need for blood transfusions before HBOT, the use of anticoagulant therapy, the number of HBO sessions, the interval between onset of hematuria and initiation of HBOT and the total radiation dose. Treatment with HBO is well tolerated, with very rare occurrence of severe and permanent side-effects. The overall quality of evidence of the studies included in the present study is low; therefore, more prospective studies are required to make accurate recommendations on the sequence of HBOT in the treatment of radiation cystitis.

Conflict of interest

None declared.

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