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ORIGINAL ARTICLE

Hyperbaric oxygen therapy for chronic radiation-induced tissue injuries: Australasia's largest study

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Abstract

***Aim*:** Chronic radiation injuries, although uncommon, are associated with poor quality of life in oncology patients. The present study assesses the efficacy and safety of hyperbaric oxygen therapy in the management of chronic radiation-induced tissue injuries.

***Methods*:** A retrospective analysis was performed in 276 consecutive patients treated with hyperbaric oxygen therapy for chronic radiation-induced tissue injuries at the Hyperbaric Medicine Unit, Townsville, Queensland, between March 1995 and March 2008. Of these patients, 189 (68%) had complete follow-up data and were assessed.

***Results*:** A total of 265 events of chronic radiation tissue injury were experienced by the 189 patients treated with hyperbaric oxygen therapy. Osteoradionecrosis prophylaxis due to radiation-induced dental disease had an overall response rate of 96% ($P = 0.00003$; Wilcoxon matched-pairs signed-rank test). The overall response rates for established osteoradionecrosis of mandible, soft tissue necrosis of head and neck, and xerostomia were 86% ($P = 0.00001$), 85% ($P = 0.002$) and 64% ($P = 0.0001$), respectively. The overall response rates for soft tissue necrosis at other sites, chronic radiation proctitis and hemorrhagic cystitis were 84% ($P = 0.03$), 95% ($P = 0.0001$) and 85% ($P = 0.03$), respectively. The total complication rate after hyperbaric oxygen therapy was 15.9%, comprising reversible ear barotrauma (10.6%), reversible ocular barotrauma (4.2%), dental complications (0.5%) and myocardial infarction (0.5%).

***Conclusion*:** Our study demonstrates that hyperbaric oxygen therapy can be effectively used in a variety of chronic radiation-induced tissue injuries; its favorable risk profile suggests it should be considered for patients with radiation-induced tissue injuries.

Key words: chronic radiation-induced toxicity, cystitis, hyperbaric oxygen therapy, osteoradionecrosis, proctitis.

INTRODUCTION

According to the World Health Organization, more than 12 million people are diagnosed with cancer every year.[1] In Australia, approximately 120 000 new cases of cancer per year are diagnosed.[2] Fifty percent of these patients should receive radiotherapy during the course of their illness, with two-thirds expected to be long-term survivors.[3,4] As more cancer patients enjoy the benefit of longer survival, there is increasing therapeutic benefit in minimizing long-term treatment morbidity.[5] Chronic radiation injuries are recognized as a factor negatively influencing quality of life in such long-term survivors.

Over the past 50 years, hyperbaric oxygen therapy (HBOT) has been used as an effective and safe treatment

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for a variety of nonmalignant conditions including severe carbon monoxide poisoning, decompression sickness and arterial embolism.[6,7] Hyperbaric oxygen has also been used in the management of various forms of chronic radiation injury.[4,8–12] A meaningful interpretation of the literature on the efficacy of HBOT in this context is complicated by the heterogeneity of the treated disease, the different types of tissue damage and the various toxicity scoring systems used. Few randomized controlled trials using HBOT for the treatment of chronic radiation injury have been attempted; nevertheless, the results appear promising for some subgroups such as head and neck patients and for those with radiation proctitis.[4,10]

We present a retrospective study examining the efficacy and safety of HBOT in the treatment of chronic radiation tissue injury. The primary aim of the study was to quantify efficacy; the secondary aim was to assess safety of HBOT in oncology patients.

METHODS

We performed a retrospective review of 276 consecutive patients treated with HBOT between March 1996 and March 2008 for chronic radiation-induced toxicities at the Townsville Hospital Hyperbaric Medicine Unit. Ethics approval was obtained from the Townsville Hospital Human Research Ethics Committee prior to commencement of the study. Tumors were staged according to the American Joint Committee on Cancer 1997.[13] Patients were excluded if there was a lack of definitive evidence that radiation exposure was the cause of symptoms, if there was likely tumor recurrence or if follow-up was incomplete. Patient risk factors, primary tumor characteristics and outcomes of cancer treatment for the included patients ($n = 189$) are summarized in Table 1.

Radiotherapy treatment

Details of radiotherapy treatment are presented in Table 2. All patients were treated with a megavoltage linear accelerator and were simulated using either conventional or computed tomography simulation. For head and neck cancer patients, most received radiotherapy in the postoperative setting ($n = 31$), with a median total dose of 64 Gy, delivered over a median of 33 fractions. The median overall treatment time was 6.4 weeks. The majority was treated with conventional photon/electron techniques ($n = 72$).

Patients with pelvic malignancy were predominantly treated with a combination of radiotherapy and hormonal therapy. The median dose of radiotherapy was 66 Gy, median number of fractions was 33 and median overall treatment time was 6.5 weeks. The majority of patients in the "other" category (94.1%) were treated postoperatively with radiotherapy with a median dose of 60 Gy.

Hyperbaric oxygen therapy

Each patient underwent an evaluation of the severity of their chronic radiation-induced injury. The attending physicians prospectively recorded the patients' specific symptoms and signs of chronic radiation-induced tissue injury as well as undertook an assessment of their fitness to undergo HBOT. Eligible patients initiated HBOT as soon as practicable, commonly within a week. Using a multiplace category 1 hyperbaric chamber, patients breathed 100% oxygen at a compression of 2.4 atmospheres absolute (ATA). Each treatment comprised 70 min of 100% oxygen inhalation, two 5-min "air breaks" and 15 min of decompression with 100% oxygen. Each patient was treated with one session per day, available 7 days per week. The number of fractions delivered depended on the clinical diagnosis. During HBOT, patients continued to receive standard supportive treatment including wound care management.

Assessment of adverse events

The site, onset and duration of the symptoms of the radiation-induced toxicities experienced as well as their severity score were diagnosed clinically and recorded according to the widely used Common Terminology Criteria for Adverse Events v3.0 (CTCAE) grading system. The chronic radiation-induced toxicities were graded according to CTCAE both prior to and after HBOT.[14] Grading into the CTCAE system was undertaken by a single radiation oncology specialist who retrospectively reviewed the cases. The duration of response to HBOT was defined as the time between the resolution of symptoms to the time of relapse of symptoms or last follow-up, whichever was sooner. The severity of radiation toxicity was classified as "severe" (score ≥ 3 on 1–5 CTCAE grading system) or "mild" (score < 3). A major response was defined as an improvement of the CTCAE score by ≥ 2 and a minor response by an improvement of the score by 1.[15] As many patients ($n = 88$; 46.6%) experienced more than one type of chronic radiation-induced toxicity, we recorded the number of these events. Complication rates attributable to HBOT were prospectively assessed post-HBOT by qualified hyperbaric medicine physicians.

Table 1 Patient and tumor characteristics

Characteristics	Head and neck	Pelvic	Others
Total patients, *n*	93	79	17
Male, *n*	76	67	5
Female, *n*	17	12	12
Median age (ranges), years	58 (26–80)	68 (37–85)	52 (41–71)
Risk factors, *n*			
Diabetes	2	6	1
Vascular disease	0	2	0
Hypertension	13	17	2
Dental extraction	3	NA	NA
IBD	1	0	0
Primary site, *n*	Mucosal H&N SCC = 71	Prostate carcinoma = 55	Breast carcinoma = 11
	Cutaneous SCC of H&N = 14	Rectal carcinoma = 11	Sarcoma of extremities = 3
	Merkel cell carcinoma = 2	Anal carcinoma = 8	CNS meningioma = 2
	Parotid AC = 1	SCC of cervix = 2	Pituitary adenoma = 1
	B-cell lymphoma = 1	TCC of bladder = 2	
	Hodgkin's lymphoma = 1	Endometrial carcinoma =1	
	Chordoma = 1		
	Cutaneous melanoma = 1		
	MPST = 1		
Stage, *n*	Stage I = 5	Stage I = 4	Stage I = 3
	Stage II = 13	Stage II = 5	Stage II = 8
	Stage III = 41	Stage III = 19	Stage III = 2
	Stage IVA = 26		Metastatic = 1
	Stage IVB = 2		Recurrence =3
	Stage IVC = 1		
	Recurrence = 4		
	NA = 1		
Outcomes of cancer treatment, *n*			
Alive, disease free	67	70	16
Alive, locoregional recurrence	11	6	0
Alive, metastasis	8	2	1
Alive, second primary	5	0	0
Dead	2	1	0

AC, adenocarcinoma; CNS, central nervous system; H&N, head and neck; IBD, inflammatory bowel disease; MPST, malignant peripheral sheath tumor; NA, not applicable; SCC, squamous cell carcinoma; TCC, transitional cell carcinoma.

Statistics

The Wilcoxon matched-pairs signed-rank test was performed to compare pre- and post-HBOT CTCAE scores for each case using StatPages.net. A two-tailed probability value of $P < 0.05$ was considered statistically significant.

RESULTS

Patient and tumor characteristics

Of the 276 consecutive patients who underwent HBOT for chronic radiation-induced injuries, 189 (68.5%) had complete follow-up data and were included in the efficacy analysis; 87 patients (31.5%) were excluded because of incomplete follow-up. Among the assessed patients, 93 received radiation therapy to the head and neck region (median age 58 years) (Table 1). Nineteen of these patients had identifiable comorbidity factors for chronic radiation-induced toxicities, including hypertension, dental extractions, diabetes and inflammatory bowel disease. The predominant primary site was mucosal head and neck squamous cell carcinoma ($n = 71$). Seventy-nine patients received radiotherapy for pelvic malignancy (median age 68 years), most commonly for carcinoma of the prostate ($n = 55$). The remaining 17 patients received radiation therapy to other body areas (breast, $n = 11$; extremity sarcoma,

Table 2 Previous oncological treatment modality details, including radiotherapy

Modalities	Head and neck ($n = 93$)	Pelvis ($n = 79$)	Others ($n = 17$)
Primary radiotherapy alone	29	27	1
Preoperative radiotherapy	2	3	0
Postoperative radiotherapy	31	0	16
Definitive concurrent chemoradiation	26	13	0
Preoperative chemoradiation	0	3	0
Postoperative chemoradiation	5	3	0
Radiotherapy + Hormone therapy	0	30	0
Radiotherapy			
Dose (Gy), median (range)	64 (36–75)	66 (25–83)	60 (40–65)
Number of fractions, median (range)	33 (9–50)	33 (5–37)	33 (6–33)
Overall treatment time (weeks), median (range)	6.4 (2.6–7)	6.5 (1–7.5)	5 (2–6.5)
Conventional fractionation, *n*	72	63	9
Hyperfractionation, *n*	4	5	1
Hypofractionation, *n*	17	7	5
High-dose rate BRT, *n*	0	2	2
Pulsed-dose rate BRT, *n*	0	1	0
3D CRT, *n*	3	7	0
Conventional photon technique, *n*	16	69	12
Conventional photon/electron technique, *n*	72	0	3
En face electron technique, *n*	2	0	0
EBRT photon + BRT technique, *n*	0	3	2

BRT, brachytherapy; EBRT, external beam radiotherapy; Gy, Gray.

$n = 3$; meningioma, $n = 2$; pituitary adenoma, $n = 1$) (Table 1).

The median interval between the completion of radiotherapy and start of HBOT was 16.9 months (range 1.6–291.2 months) for head and neck patients, 18.9 months (2.7–121.4 months) for the pelvic group and 23.4 months (1.2–68.9 months) for the other patients. The median follow-up for the assessed patients was 3.8 years, defined as the time from symptom resolution to the time of relapse or last review of patients yet to experience any relapse. One hundred fifty-three patients (81%) were alive and free of disease, 17 patients (9%) were alive with locoregional recurrences and 11 patients (6%) were alive with metastatic disease. The remaining patients were alive with a second primary cancer (five patients) and one patient died from metastatic disease.

A total of 265 cases of chronic radiation injury were experienced by the 189 patients. Of these, 153 cases (58%) were experienced by the 93 patients who received radiotherapy to the head and neck area; 94 cases (35%) occurred in the 79 patients who received radiotherapy to the pelvis. The remaining 18 cases (7%) of chronic radiation injury were experienced by 17 patients who received radiotherapy to other sites.

Outcomes for head and neck patients

Outcomes of HBOT for chronic radiation injury of head and neck region are presented in Table 3. Thirty-two cases showed an improvement in xerostomia, giving an overall response rate of 64% ($P = 0.002$). Three cases (6%) showed a major response with a median duration of response of 27 months (26–36 months). Two of the three instances of major improvement were seen in severe cases and one in a mild case of xerostomia (category 2). Twenty-nine cases (58%) had a minor response with a median duration of 26 months (2–94 months). The remaining 18 cases (36%) did not respond to HBOT. Xerostomia progression was noted in two patients (6%).

There were 35 cases of osteoradionecrosis (ORN) of the mandible who underwent HBOT. The overall response rate was 89% ($P = 0.00001$). Twenty-seven cases (77%) had a major response with a median duration of response of 22 months (2–108 months). Four cases (11%) showed a minor response with a median duration of response of 22 months (4–39 months). Two cases (6%) did not respond to HBOT, and the remaining 2 cases (6%) progressed on HBOT.

Table 3 Outcomes of HBOT for chronic radiation injury of the head and neck

Type and number of cases (*n*)	Major response		Minor response		No response *n* (%)	Progression *n* (%)	Overall response rate % (*P*-value)
	Number of cases (response rate %)	Median and range duration of response (months)	Number of cases (response rate %)	Median and range duration of response (months)			
Xerostomia (50)	3 (6%)	27 (26–36)	29 (58%)	26 (2–94)	18 (36%)	2(6%)	64% ($P = 0.0001$)
ORN of mandible (35)	27 (77%)	22 (2–108)	4 (11%)	22 (4–39)	2 (6%)	2(6%)	89% ($P = 0.00001$)
ORN of auditory canal (2)	1 (50%)	33 (NA)	1 (50%)	27 (NA)	–	–	100% (NA)
ORN of maxilla (1)	1 (100%)	2 (NA)	–	–	–	–	100% (NA)
ORN of mastoid (1)	–	–	1 (100%)	10 (NA)	–	–	100% (NA)
ORN prophylaxis (24)	22 (92%)	26 (1–78)	1 (4%)	15 (NA)	1 (4%)	–	96% ($P = 0.00003$)
H&N soft tissue necrosis (12)	7 (58%)	25 (2–116)	3 (25%)	11 (3–12)	2 (17%)	–	83% ($P = 0.002$)
Neck fibrosis (7)	1 (14%)	36 (NA)	4 (57%)	36 (9–56)	2 (29%)	–	71% ($P = 0.125$)
Dysphagia (6)	–	–	3 (50%)	25 (7–26)	3 (50%)	–	50% (NA)
Dental disease (3)	1 (33%)	21(NA)	–	–	2 (67%)	–	33% (NA)
Keratitis (2)	–	–	1(50%)	21(NA)	1 (50%)	–	50% (NA)
Esophageal stricture (2)	1 (50%)	45 (NA)	1 (50%)	26 (NA)	–	–	100% (NA)
CNS necrosis (2)	1 (50%)	17 (NA)	1 (50%)	10 (NA)	–	–	100% (NA)
Stomatitis (2)	1 (50%)	34 (NA)	1 (50%)	17 (NA)	–	–	100% (NA)
H&N fistula (1)	–	–	–	–	1 (100%)	–	NA
Deafness (1)	–	–	1 (100%)	25 (NA)	–	–	100% (NA)
Facial pain (1)	–	–	1 (100%)	34 (NA)	–	–	100% (NA)
Oral cavity pain (1)	–	–	1 (100%)	9 (NA)	–	–	100% (NA)

CNS, central nervous system; H&N, head and neck; NA, not applicable; NS, not significant; ORN, osteoradionecrosis.

The overall response rate of ORN prophylaxis for radiation-induced dental caries was 96% ($P = 0.00003$). Twenty-two cases had a major response with a median duration of response of 26 months (1–78 months). One case had a minor response and one case did not respond to HBOT.

There were 12 cases of soft tissue necrosis in the head and neck area. The overall response rate was 83% ($P = 0.002$). Seven cases (58%) achieved a major response with a median duration of response of 25 months (2–116 months); three cases (25%) had a minor response with a median duration of response of 11 months (3–12 months). The remaining two cases (17%) did not respond to HBOT.

Outcomes for pelvis/other sites

The outcomes of HBOT for chronic radiation injury of the pelvis and other sites are presented in Table 4. There were 59 cases of radiation-induced proctitis experienced by 79 patients who received pelvic irradiation. The overall response rate of proctitis to HBOT was 95% ($P = 0.0001$). Thirty-one cases (51%) had a major response with a median duration of response of 15 months (2–76 months). Twenty-five cases (42%) had a minor response with a median duration of response of 20 months (1–84 months). Three cases (5%) did not respond to HBOT.

There were 20 cases of radiation-induced cystitis. The overall response rate was 85% ($P = 0.003$). Six cases (30%) had a major response with a median duration of response of 11 months (1–20). Eleven cases (55 %) had a minor response and three cases (15%) had no response. The median duration of the minor response was 15 months (2–84 months).

There were seven cases of soft tissue necrosis from irradiation to other sites. The overall response rate was 84% ($P = 0.03$), four cases (57%) had a major response, two cases (29%) had a minor response and one case (14%) had no response. The median duration of response was 24 months (1–63) and was 19 months (16–22) for major and minor responses, respectively.

Complication rates of HBOT

Among the 189 patients analyzed, 29 experienced 30 complications arising from HBOT (Table 5). Ear barotrauma was the most common side effect, occurring in 20 patients (10.6%). Of these, nine patients had grade 1, ten patients had grade 2, and one patient had grade 3 ear barotrauma. This side effect was reversible and none of the patients had permanent ear toxicity. Eight patients

Table 4 Outcomes of HBOT for chronic radiation injury of the pelvis and other sites

Type and number of cases (*n*)	Major response		Minor response		No response *n* (%)	Progression *n* (%)	Overall response rate % (*P*-value)
	Number of cases (response rate %)	Median and range duration of response (months)	Number of cases (response rate %)	Median and range duration of response (months)			
Proctitis (59)	31 (51%)	15 (2–76)	25 (42%)	20 (1–84)	3 (5%)	–	95% ($P = 0.0001$)
Cystitis (20)	6 (30%)	11 (1–20)	11 (55%)	15 (2–84)	3 (15%)	–	85% ($P = 0.003$)
ST necrosis (7) [Breast (4), skeletal (3)]	4 (57%)	24 (1–63)	2 (29%)	19 (16–22)	1 (14%)	–	84% ($P = 0.03$)
Urethral stricture (5)	1 (20%)	70 (NA)	3 (60%)	24 (16–69)	–	1(20%)	80% (NA)
Pelvic ST necrosis (4)	3 (75%)	10 (9–12)	1 (25%)	14 (NA)	–	–	100% (NA)
Wound healing complications (4)	4 (100%)	6 (2–30)	–	–	–	–	100% (NA)
Anal stricture (1)	1 (100%)	20 (NA)	–	–	–	–	100% (NA)
Perineal pain (1)	1 (100%)	35 (NA)	–	–	–	–	100% (NA)
Breast pain (4)	2 (50%)	6 (4–9)	2 (50%)	23 (3–43)	–	–	100% (NA)
Chest wall fibrosis (2)	–	–	2 (100%)	15 (6–24) < >	–	–	100% (NA)
ORN of ribs (1)	–	–	1 (100%)	3 (NA)	–	–	100% (NA)
Memory impairment (1)	–	–	1 (100%)	68 (NA)	–	–	100% (NA)
Proctocolitis (1)	–	–	–	–	1 (100%)	–	–
Thigh pain (1)	1 (100%)	180 (NA)	–	–	–	–	100% (NA)
Optic neuropathy (1)	–	–	1 (100%)	10 (NA)	–	–	100% (NA)

CNS, central nervous system; H&N, head and neck; NA, not applicable; NS, not significant; ORN, osteoradionecrosis; ST, soft tissue.

Table 5 Rate of complications following HBOT for chronic radiation injury[14]

Complication[†]	Head and neck patients[‡] ($n = 93$)	Pelvic patients ($n = 79$)	Other patients ($n = 17$)	All patients ($n = 189$)
Ear barotrauma, *n*	10	8	2	20 (10.6%)
Eye barotrauma, *n*	4	3	1	8 (4.2%)
Dental, *n*	0	1	0	1 (0.5%)
Myocardial infarct, *n*	1	0	0	1 (0.5%)
Oxygen toxic seizure, *n*	0	0	0	0
Death, *n*	0	0	0	0
Total, *n*	15	12	3	30 (15.9%)

[†]Adverse events attributable to HBOT rather than chronic radiation tissue injury are summarized here. [‡]Only patients for whom complete follow-up data were available are included in this table ($n = 189$). HBOT, hyperbaric oxygen therapy.

(4.2%) experienced reversible myopia; one of these patients (0.5%) also had a toothache. One patient (0.5%) experienced a myocardial infarct while having HBOT for established ORN of the mandible.

As noted above, 87 patients (31.5%) were not included in the analysis of the efficacy of HBOT in chronic radiation injury because of incomplete follow-up data. One of the excluded patients had a myocardial infarct while having HBOT for established ORN of the mandible. Another patient with no apparent seizure-predisposing factors had a seizure after 25 sessions of HBOT for CNS necrosis. This patient was treated with antiseizure medication and did not have any further long-term complications. A further patient with a myelodysplastic syndrome died of the condition after receiving eight sessions of HBOT.

DISCUSSION

Our study demonstrates that HBOT can be an effective treatment for a wide variety of chronic radiation-induced tissue injuries. The range of conditions and the subtypes of chronic radiation injuries for which HBOT was used were similar to the published literature.[6–9,11,12] While the majority of cases showed clinical improvement after HBOT, a statistically significant improvement

was seen only in certain types of injury including xerostomia, ORN prophylaxis, ORN of the mandible, soft tissue necrosis and radiation proctitis or cystitis.

Xerostomia is a common side effect of head and neck radiation therapy with a significant negative impact on patients' quality of life.[16–19] Xerostomia impairs oropharyngeal function and may be associated with dental disease and oral infections.[17] Previous studies have suggested that HBOT may be effective in ameliorating the effects of radiation-induced xerostomia.[17–22] In order to further evaluate the efficacy of treatment, we differentiated between minor and major responses to treatment. Nearly two-thirds of our patient cohort with this condition responded positively to HBOT (response rate 64%); however, the majority of the responses were of the "minor" category. The majority of our cases had mild xerostomia and therefore had less scope for improvement: pleasingly, we saw a major improvement in two of the three cases with severe xerostomia.

The ORN of the mandible is an uncommon but morbid complication of radiotherapy for head and neck cancer.[12,23] ORN is difficult to treat and outcomes are often poor. Risk factors for developing ORN include dental extraction, dental disease and a radiation dose of more than 60 Gy.[8,24,25] Our findings support consideration of HBOT prior to dental extraction for patients who are to receive high-dose radiation (our patients received a median dose of 64 Gy) to the head and neck area. The majority of patients with severe radiation-induced dental disease required complete dental clearance. It is therefore pleasing to note that the majority of patients in the ORN prophylaxis group had a major response to HBOT (92%). The rate of ORN post-dental extraction in the prophylactic group was 4% (the one case that did not respond to HBOT). Although the numbers are small, our rate of ORN after prophylactic HBOT prior to dental extraction is comparable to rates reported in other studies (2–6%).[8,24–26] Importantly, the incidence of ORN in patients undergoing post-radiation tooth extraction without HBOT is 6.9%, and highest in those receiving more than 60 Gy (12.2%).[25] Thus, our study would support a consideration of HBOT in preventing ORN in high-risk patients.[4]

Our results in 35 cases of established ORN of the mandible are in line with other retrospective studies.[8,9,27–29] There was a significant improvement in ORN with an overall response rate of 89%; 27 cases (77%) had almost complete resolution of the mandibular necrosis treated with HBOT alone. These improvements are similar to those of Hampson *et al.* who recently reported resolution in 73% of patients and a significant improvement in a further 21%, almost always in conjunction with surgery.[29] A review of available retrospective series by Feldmeier reported that the recovery rate of ORN treated with HBOT alone was 15–45%; HBOT combined with surgery resulted in recovery rates of 20–90%.[8,9] In contrast, the only prospective double-blind randomized controlled trial conducted by Annane *et al.* showed no beneficial effect of HBOT in treatment of overt mandibular ORN, and in fact the HBOT arm had worse outcomes.[27] It was speculated that the worse outcome of Annane *et al.'s* HBOT arm was due to a better recovery rate in the placebo group due to better conservative management. The reason for favorable outcomes with HBOT for established ORN of the mandible in our uncontrolled study (and the literature) may be due in part to retrospective bias; hence, ours and other's positive results should not be used in isolation to support the *routine* use of HBOT in this context. However, the single trial of Annane *et al.*[27] may be insufficient to influence clinical practice and it would seem reasonable to continue to consider HBOT for individual cases of established ORN of the mandible pending further controlled trials.[9,28]

Several retrospective studies suggest that HBOT is an effective treatment for soft tissue radionecrosis.[8,9] So far, there has been no randomized trial addressing the effectiveness of HBOT in this setting. We found a significant improvement of head and neck soft tissue necrosis in 10 of 12 cases treated with HBOT, giving an overall response rate of 83%. Seven cases (58%) had sustained major responses resulting in complete resolution of the ulcers (median duration of response 25 months). Similar improvements with HBOT were noted for soft tissue necrosis at other sites (four breast and three skeletal; overall response rate 84%). These improvements are consistent with the notion that high oxygen tension promotes neovascularization in radiation-damaged tissue.[4,7]

HBOT for the treatment of chronic radiation-induced proctitis (CRP) has shown promising results.[9,12,29–32] We report a clinical response rate for CRP of 95%, where around half of the cases had a durable major response, with some patients experiencing symptom relief lasting as long as 7 years. These response rates compare favorably with earlier studies summarized by Feldmeier: a total of 86% of patients with proctitis, colitis and enteritis had complete resolution, while 41% demonstrated at least a partial response.[9] In a prospective randomized blinded trial, Clarke *et al.* investigated the effect of HBOT on CRP with an average follow-up of 2 years.[31]

The response rate was significantly better in the HBOT arm compared with the sham arm (1.1 ATA air) (88.9% *vs* 62.5%, respectively). In addition, quality of life was markedly improved in the HBOT arm prior to crossover.

Radiation-induced hemorrhagic cystitis (RIHC) is a rare complication of radiotherapy for prostatic, bladder, rectal and gynecological malignancies; severe forms may be associated with significant morbidity.[8,29,33–37] The majority of studies examining the efficacy of HBOT for RIHC are retrospective case series,[8,33–37] with the exception of a prospective study by Bevers *et al*.[36] Collating the data, Feldmeier reported that 76.3% of patients showed either partial or complete response to HBOT.[9] Recently, Hampson *et al*. reported that 57% of patients with radiation cystitis had a complete resolution and another 32% a significant improvement, yielding an overall response rate of 89%.[29] The overall response rate in our study was similar at 87%.[8,12,33–37] The long-term efficacy of HBOT for treatment of RIHC, however, remains questionable.[35] We found that the resolution of hematuria was relatively long-lasting, with a median duration of response of 15 months. Recurrence of hematuria can be treated with a repeat course of HBOT,[35,36] although the recommended optimum number of sessions of HBOT to alleviate the symptoms of RIHC (40) represents a substantial commitment in time and resources.

The potential risk-benefit ratio of HBOT for treatment of chronic radiation-induced tissue injuries has often been overstated.[7,11,12,29] In our study, the overall complication rate was 15.9%. Not surprisingly, ear barotrauma was the most commonly encountered complication (10.6%), followed by reversible eye barotrauma, dental complications and one myocardial infarct. These complication rates compare favorably with reported series: 15–20% for symptomatic reversible ear barotrauma; up to 20% for reversible optic symptoms; 15–20% for pulmonary symptoms; and 1–2% for severe central nervous symptoms.[7] Hampson *et al*. found HBOT to be "quite safe" for their patients with chronic radiation tissue injury; none stopped therapy because of ear barotrauma or symptomatic oxygen-induced myopia.[29] Giebfried *et al*. included 90 patients who received HBOT for head and neck cancer. The risks of stroke and myocardial infarct over 15 years for both were 1.1%.[38] Our low complication rates could perhaps be due to underreporting because the follow-up data of 89 patients who were excluded from final analyses were not fully assessable. Myer *et al*. reported one patient died after 10.5 months of HBOT due to myelodysplasia.[30] Similarly, we had one patient who had myelodysplasia and died after eight sessions of HBOT; however, this patient was an exclusion and was not included in our study group.

The theoretical potential to increase risk of cancer recurrence with HBOT is often raised[39,40]; we did not see it here. In our study, 81.0% of patients were alive and disease free (at last follow-up); 8.5% were alive with locoregional recurrence; 5.8% were alive with distant metastasis; and 2.6% were alive with a second primary tumor. We were not able to obtain a control group to establish whether HBOT contributed to inferior outcomes of the cancer treatment. Several literature reviews on the effect of hyperbaric oxygen on cancer growth have been published.[7,9,10,39,40] The general consensus is that hyperbaric oxygen has a neutral effect on tumor growth; in fact, some evidence suggests that hyperbaric oxygen may have a negative impact on malignant tumor progression or formation.[40]

It should be noted that our study, which was conducted over a period of 13 years, has several limitations due to its retrospective nature. The assessment of the chronic radiation-induced tissue injuries was based on clinical record information only; however, the treating hyperbaric oxygen physician and the patients had *prospectively* documented the progress of the major symptoms on HBOT, allowing for reasonable confidence in the accuracy of the treatment response. As pointed out by Bui *et al*., it is possible that some of the chronic radiation-induced toxicities experienced by the patients might spontaneously improve over time without HBOT.[15] Spontaneous improvements were not controlled for in this study. Furthermore, the study was underpowered for some types of chronic radiation tissue injury and had a large number of excluded patients; however, it is one of the largest studies to date.

CONCLUSION

Our retrospective study indicates that HBOT is an effective treatment modality for a variety of chronic radiation-induced tissue injuries and is associated with a low complication rate. Patients treated with HBOT showed significant improvements in xerostomia, ORN prophylaxis and ORN of the mandible, soft tissue necrosis, chronic radiation proctitis and RIHC. In the majority of cases, the improvement in these conditions was sustained through a median follow-up period of 3.8 years. The favorable risk profile of this therapy suggests that HBOT should be considered as a viable treatment option for oncology patients, particularly

those with, or at high risk of, radiation-induced tissue injuries.

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