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CLINICAL INVESTIGATION **Normal Tissues**

THE EFFICACY OF HYPERBARIC OXYGEN THERAPY IN THE TREATMENT OF RADIATION-INDUCED LATE SIDE EFFECTS

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Purpose: **We investigated the efficacy of hyperbaric oxygen therapy (HBOT) in the management of patients with radiation-induced late side effects, the majority of whom had failed previous interventions.**
Methods and Materials: **Of 105 eligible subjects, 30 had either died or were not contactable, leaving 75 who qualified for inclusion in this retrospective study. Patients answered a questionnaire documenting symptom severity before and after treatment (using Radiation Therapy Oncology Group criteria), duration of improvement, relapse incidence, and HBOT-related complications.**
Results: **The rate of participation was 60% (45/75). Improvement of principal presenting symptoms after HBOT was noted in 75% of head-and-neck, 100% of pelvic, and 57% of "other" subjects (median duration of response of 62, 72, and 68 weeks, respectively). Bone and bladder symptoms were most likely to benefit from HBOT (response rate, 81% and 83%, respectively). Fifty percent of subjects with soft tissue necrosis/mucous membrane side effects improved with HBOT. The low response rate of salivary (11%), neurologic (17%), laryngeal (17%), and upper gastrointestinal symptoms (22%) indicates that these were more resistant to HBOT. Relapse incidence was low (22%), and minor HBOT-related complications occurred in 31% of patients.**
Conclusion: **Hyperbaric oxygen therapy is a safe and effective treatment modality offering durable relief in the management of radiation-induced osteoradionecrosis either alone or as an adjunctive treatment. Radiation soft tissue necrosis, cystitis, and proctitis also seemed to benefit from HBOT, but the present study did not have sufficient numbers to reliably predict long-term response.** **© 2004 Elsevier Inc.**

Hyperbaric oxygen therapy, Radiation late side effects, Osteoradionecrosis, Response.

INTRODUCTION

Radiation is a therapeutic modality commonly used in the management of cancer. Although most patients experience some acute side effects, it is a rare and serious event when severe late side effects develop (1). Acute side effects during or in the immediate postirradiation period are mostly self-limiting or amenable to simple medical management. On the other hand, late side effects, occurring after this period, are slower to heal and may lead to chronic debility. For example, osteoradionecrosis is one serious late effect present in the minority of head-and-neck cancer patients treated with radiation. Although 85% of cases resolve with conservative management, the remainder become refractory and can progress to involve a more extensive area of bony and soft tissue (2).

In recent years, our understanding of the underlying mechanisms of late radiation-induced side effects has increased (3–7). Although cellular depletion and tissue devascularization were originally thought of as being the predominant pathologic basis for these side effects (8), they represent merely a histopathologic marker for a far more complex and clinically diverse problem (9). Both patient- and treatment-related factors seem to contribute to this process. It is now known that the size of the radiation treatment field, dose per treatment, and total dose are important factors that are associated with the occurrence of radiation-related side effects (10, 11). Also different tissues have various levels of tolerance to radiation damage, possibly because of the structural organization of that tissue. More specifically, tissues whose functional subunits are arranged in series tend to display a lower degree of radiation tolerance than those with parallel arrangement, because serially arranged subunits depend on the well-being of all subunits before and after them (12). Patients' comorbid disease may also affect the ability to repair tissue damage caused by therapeutic radiation. Anecdotal data suggest a possible correlation between connective tissue diseases and

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Table 1. Basic demographics of participating patients

Total patients (*n*)	Male (*n*)	Female (*n*)	Median age/range (years)	Head and neck (*n*)	Pelvic (*n*)	Other sites (*n*)
45	28	17	64 (7–88)	31	7	7

increased radiosensitivity (13), though clinical evidence thus far has not conclusively confirmed any such relationship (14). Recent evidence suggests a role of an impaired genomic repair capacity of radiation-induced DNA damage in some patients with severe radiation-related late side effects (15).

Hyperbaric oxygen therapy (HBOT) has been used in the past to assist in the repair of radiation-induced damage (8). Besides improving temporarily the oxygenation of tissue and helping eradicate anaerobic bacteria, it is thought that high oxygen tension promotes neovascularization in damaged tissues of radiation-treated patients (16). Studies have shown that HBOT effectively treats irradiated soft tissue necrosis (17, 18) and has also been used empirically to treat mandibular osteoradionecrosis, radiation cystitis, radiation proctitis, and other radiation side effects (19–28). HBOT has also been used for the other areas of problematic wound healing, such as ulcers in chronic diabetes and burns, besides its obvious role in the treatment of decompression disease (29, 30).

Certain chemotherapies sensitize cells to effects of radiation through various mechanisms (31–33). Combination chemoradiotherapy plays a valuable role in tumor downstaging, increasing surgical resectability, and potentially improving long-term prognosis (34, 35). However, associated with enhancing tumor response is a potentially equal sensitization of normal tissues to radiation resulting from a biologically more intense treatment. Recent data suggest that more intense therapy may prolong acute symptoms, leading to consequential late effects (36).

In this retrospective study, we aim to evaluate the efficacy of HBOT in the treatment of radiation-induced late side effects in a group of patients treated with radiation alone or in combination with chemotherapy.

METHODS AND MATERIALS

This study was granted institutional review board approval at UCLA in accordance with the Health Insurance Portability and Accountability Act of 1996. We recruited patients who were treated between January 1998 and August 2003 at the UCLA Hyperbaric Oxygen Unit for radiation late effects. From these patients we received written permission to access their medical records. Our inclusion criteria required that patients must have received radical radiation for their cancers or noncancerous condition that consequently led to serious late side effects within the irradiated area. In addition, the side effects needed to have been thoroughly investigated to exclude tumor recurrence and to determine that they were the result solely of radiation treatment. Symptoms were classified as being acute (less than 6 months) or late (more than 6 months). Patients could have sought and failed medical treatments before HBOT. The medical treatments may have included steroids (oral or cream), nonsteroidal anti-inflammatory drugs, antidiarrheal agents, local anesthetics, and sometimes surgery. Patients were then referred for HBOT with the sole intention of relieving radiation-related symptoms. Lacking definitive evidence that radiation exposure was the cause of symptom development constituted grounds for exclusion. Likewise, having a possible link of symptoms to tumor regrowth/necrosis also made subjects ineligible for our study. Age, gender, pregnancy or childbearing potential, and racial/ethnic origin were not criteria for exclusion in this study.

One hundred five subjects were considered eligible for this study. Twenty patients no longer resided at the same address and were not contactable. Ten subjects had died, leaving a pool of 75 subjects whom we were able to contact for participation in the study. Basic demographics of these patients are outlined in Table 1. Table 2 describes past cancer diagnoses, the type of cancer treatments, and any past medical and/or surgical management of radiation-induced side effects. The patients answered a telephone questionnaire that was designed to extract information regarding subjective evaluation of their progress on the HBOT delivered at UCLA. The questions aimed to elicit the timing and duration of acute and late symptom development from radiation treatment, post-HBOT symptom relief, and/or relapse. Patient respondents were then sent an authorization form, which they signed to grant the research team access to their UCLA medical records. For 1 pediatric patient, the parents answered questions and authorized the release of medical records on the patient's behalf. Using the subjects' symptom description and presenting history, we determined the severity of radiation-induced late side effects by assigning each a score based on the Radiation Therapy Oncology Group (RTOG) late effects grade (37). We recorded the site and duration of the symptoms experienced as well as their severity scores. Acute complications due to HBOT were routinely recorded during the subjects' treatment course by the treating staff of the Hyperbaric Unit (Table 3).

Duration of response to HBOT was defined as the time of symptom resolution to the time of relapse or to October 2003 for subjects yet to experience any relapse. In general, symptom improvement denoted *any* decrease in symptom scores ≥ 1 on the RTOG late radiation side effects score. Response of specific symptoms to HBOT was also documented to determine the HBOT differential efficacy. For analytical purposes, the severity of radiation-induced late side effects was separated into "severe" (score 3 on the 0–4

Table 2. Past cancer treatments and non-HBOT management of radiation-induced late side effects

		Head-and-neck patients (n = 31)	Pelvic patients (n = 7)	Others (n = 7)
Past cancer treatments	Radiation alone	6	3	1
	Radiation/chemotherapy	4	0	1
	Radiation/surgery	15	3	2
	Radiation/chemotherapy/surgery	6	1	3
Past management of radiation-induced late side effects	Antibiotic treatment	16	2	3
	Pain medication	5	0	1
	Steroid treatment	5	0	0
	Surgery	13	0	2
	Others	0	2	0
Response to past non-HBOT treatments of radiation-induced late side effects (n = 37)*	With improvement	6	0	3
	Without improvement	20	4	4

Abbreviation: HBOT = hyperbaric oxygen therapy.
*Of all 45 subjects, 37 had received non-HBOT treatments for late symptoms.

RTOG scoring scheme) and "mild" (score <3). Major responders were defined as patients who experienced a decrease in RTOG symptom score ≥2 as a result of HBOT, and minor responders were those with symptom improvement of the RTOG score equal to 1. At presentation for HBOT, most subjects, in addition to their principal presenting symptom, described other radiation side effects. Therefore, the degree of improvement of incidental symptoms was also analyzed to maximize the patient pool for each specific symptom. Relapse incidence was obtained for each patient group by comparing the number of subjects with post-HBOT symptom recurrence to the number of those with post-HBOT symptom improvement in each respective group.

RESULTS

From 75 eligible subjects, a total of 45 patients responded to the questionnaire (overall response rate of 60%). Of these, 31 patients (69%) had irradiation for head-and-neck (H&N) cancer. We also included in this group 3 patients with brain irradiation for past brain cancer diagnoses who experienced radiation-related late effects in the head-and-neck region (Table 1). Seven patients (16%) received radiation therapy to the pelvic area (prostate n = 5, uterus n = 1, and ovarian/perineum n = 1). The remaining 7 patients received radiation treatment to other body areas (breast n = 1, limb sarcoma n = 2, limb noncancerous dermatologic problem n = 1, Hodgkin's lymphoma of the chest n = 1, large-cell lymphoma of chest n = 1, malignant histiocytoma of back n = 1). Before HBOT, all but 8 patients had undergone medical and/or surgical management in the past for treatment of the radiation-induced late side effects. The treatments included different combinations of medication, debridement, skin graft and/or bone graft; of these, only 9 of the 37 patients (24%) reported minor improvement of their symptoms (Table 2).

Table 3. Acute side effects experienced by patients on hyperbaric oxygen therapy

Hearing	Vision	Epistaxis
10/45 (22%)	3/45 (6.7%)	1/45 (2.2%)

No serious, life-threatening complication arose from HBOT. A small number of patients experienced minor side effects (Table 3). Auditory problems were most common (22%), and these ranged from hearing difficulties to ear pain during or shortly after HBOT. Only 1 patient had a serous effusion in 1 ear. No subjects in this study reported any persistent residual hearing problems. Three patients experienced visual complications: One patient developed lens swelling, and the other 2 patients experienced accelerated cataract formation. Lens swelling was short-lived, because the patient received ophthalmologic clearance to continue HBOT. Patients with accelerated cataract formation subsequently underwent surgery without additional problems. One patient suffered an episode of epistaxis, which never recurred on subsequent HBOT sessions.

As illustrated in Table 4, 10 of 31 H&N patients (32%) received HBOT in conjunction with surgical procedures such as debridement, bone graft, and skin graft, respectively. This combination usually entails 20–30 preoperative HBOT sessions (5 sessions per week at 2.4 atmosphere absolute (ATA) for 100 min each), followed by surgery and concluded with 10–15 postoperative HBOT sessions. The remaining patients did not receive surgery as part of the management of their radiation-induced late side effects. All patients (H&N as well as non-H&N) who were receiving steroid, antibiotic, or pain medications before HBOT continued their medications during the course of HBOT, regardless of surgery plan or lack thereof. In each patient

Table 4. Overall response to hyperbaric oxygen therapy

	Response of principal presenting symptom of HBOT	Head-and-neck patients (n = 31)	Pelvic patients (n = 7)	Others (n = 7)
Overall	With overall improvement	21 (75%)	7 (100%)	4 (57%)
	Without improvement	7 (25%)	0	2 (29%)
	Number of patients receiving HBOT for prophylaxis	3	0	0
Patients receiving HBOT and surgery	With overall improvement	8	0	0
	Without improvement	2	2	0
Patients receiving HBOT alone	With overall improvement	13	7	4
	Without improvement	5	0	2
Median number of HBOT sessions (range)		30 (15–60)	40 (20–60)	40 (25–57)

Abbreviation: HBOT = hyperbaric oxygen therapy.

group (H&N, pelvic, and others), the percentage of subjects who received concurrent medical treatment (steroid, pain, and/or antibiotic medications) during HBOT approximately equals that of subjects without such medications. Thirty-eight percent of the H&N group that experienced post-HBOT improvement of their principal presenting late side effects received a combination of HBOT and surgery, compared to 62% of the H&N group that improved on HBOT alone. All pelvic patients and 4 of 7 patients with other past cancer diagnoses responded favorably to HBOT alone (100% and 57%, respectively) (Table 2). The median duration of response to HBOT alone or HBOT with adjunct surgery ranged from 62 weeks for H&N subjects to 72 weeks for pelvic subjects. Overall post-HBOT relapse (signifying the recurrence of symptoms with severity similar to the pre-HBOT level) among all 32 subjects with post-HBOT improvement was 22% (Table 5).

Symptoms least likely to benefit from HBOT included salivary (11%), laryngeal (17%), neurologic (17%), and gastrointestinal (GI) (22%) late side effects. GI symptoms include those of the upper GI tract, mostly the result of esophageal fibrosis, and those of the lower GI tract secondary to radiation proctitis. Whereas the latter responded well to HBOT, the former were much more resistant to the same treatment with only 1 of 14 patients showing any improvement at all. In contrast, 17 of 21 subjects (81%) with bone symptoms such as mandibular or pelvic osteoradionecrosis benefited from HBOT with or without surgery. Seven of 17 subjects (41%) with improvement of bone symptoms received the combined treatment of preoperative HBOT, surgery, and postoperative HBOT, commonly known as the Marx protocol (38). The remaining 10 subjects (56%) showed bone symptom improvement after HBOT alone. Similarly, 5 of 6 subjects (83%) with radiation-induced cystitis benefited from HBOT alone.

One subject with radiation-induced and superimposed fungal pneumonitis improved on a combination of HBOT and amphotericin B treatment. About half of all subjects with skin, s.c., or mucous membrane late side effects noticed improvement of their respective symptoms (Table 6). Most patients with improvement of these symptoms benefited from HBOT alone. In fact, only 1 subject who was successfully treated for skin and s.c. symptoms required HBOT in conjunction with a skin flap procedure. It is also worth noting that major responders outnumber minor responders in all symptom categories, except, as expected, for salivary and neurologic symptom groups (Table 6). Post-HBOT relapse incidence of each specific symptom was also

Table 5. Post-HBOT incidence of symptoms relapse*

	Head-and-neck subjects	Pelvic subjects	Others
Number of subjects with post-HBOT improvement	21	7	4
Number of subjects with relapse post-HBOT	4	3	0
Relapse incidence	19%	43%	0%
Overall median duration of symptom improvement	62 weeks (3–260)	72 weeks (4–106)	68 weeks (4–130)
Median duration of symptom improvement among subjects with relapse	33 weeks (8–52)	8 weeks (4–78)	NA

Abbreviation: HBOT = hyperbaric oxygen therapy.

* Relapse incidence was calculated from the ratio of the number of patients with symptom recurrence after HBOT to the total number of patients with post-HBOT improvement in each group.

Table 6. Patients with durable symptom (RTOG) improvement post HBOT*

	Skin ($n = 14$)	Subcutaneous ($n = 13$)	MM ($n = 4$)	Salivary ($n = 19$)	Bone ($n = 21$)	Larynx ($n = 6$)	Bladder ($n = 6$)	Neuro ($n = 6$)	GI ($n = 18$)	Lung ($n = 1$)
Patients with severe sx's (G $\geq$ 3, on scale 0–4)	9	10	2	11	21	2	3	4	4	1
Patients with mild sx's (G $<$ 3, on scale 0–4)	5	3	2	8	0	4	3	2	14	0
Total number of patients with improvement from HBOT	8 (57%)	6 (46%)	2 (50%)	2 (11%)	17 (81%)	1 (17%)	5 (83%)	1 (17%)	4 (22%)	1 (100)%
Major responders (sx grade improvement of 2 or more after HBOT)	5 (36%)	5 (38%)	2 (50%)	1 (5%)	15 (71%)	1 (17%)	3 (50%)	0	4 (22%)	1 (100%)
Minor responders (sx grade improvement of 1 after HBOT)	3 (21%)	1 (8%)	0	1 (5%)	2 (10%)	0	2 (33%)	1 (17%)	0	0
Patients without response to HBOT	5 (36%)	6 (46%)	2 (50%)	17 (90%)	4 (19%)	5 (83%)	1 (17%)	5 (83%)	14 (78%)	0
Relapse	1 (12%)	1 (17%)	0	0	4 (25%)	0	2 (40%)	0	1 (25%)	0

Abbreviations: RTOG = Radiation Therapy Oncology Group; HBOT = hyperbaric oxygen therapy; MM = mucous membranes; GI = gastrointestinal; sx = side effect; G = grade.

* These include both principal presenting symptoms, for which HBOT was indicated, and other related symptoms.

documented in Table 6. No difference in the response rate to HBOT of principal presenting symptoms was observed among subjects treated with radiation therapy alone and those with chemoradiation in the past.

DISCUSSION

We found that the majority of patients with radiation-induced late side effects showed improvement after either HBOT alone or HBOT followed by surgical or medical procedures. HBOT facilitated symptom improvement in all patients with pelvic symptoms, 4 of 7 patients (57%) with "other" symptoms, and the majority of H&N patients with late side effects (75%) (excluding 3 subjects treated with HBOT prophylactically). We were unable to obtain a control group in this study, because HBOT has currently become a common recommendation for most patients with radiation-induced late side effects (39). We did note, however, that the majority of all subjects did receive non-HBOT medical (antibiotics, pain medication, anti-inflammatory agents) and/or surgical managements (debridement, skin flap and bone implant procedures) of their symptoms before referral for HBOT. Some patients benefited from these treatments but subsequently suffered relapse of the same symptoms, whereas others did not notice any improvement whatsoever or did so only to an unsatisfactory extent.

Osteoradionecrosis appeared to be highly responsive to HBOT (81%) (Table 6). This is a very difficult condition to treat, especially when the necrotic or fractured bone tissue incurs superimposed infection. In the present study, the majority of H&N patients had already received lengthy courses of antibiotic treatment before HBOT was initiated. Among H&N subjects who showed favorable response of bone or nonbone symptoms to HBOT (21 of 28), a higher percentage improved after HBOT alone (62%) compared to the combined treatment of HBOT and surgery (38%). This is likely to relate to the selection based on the severity of symptoms that necessitated surgical procedures. All 13 H&N patients who received the Marx protocol presented with Grade 4 principal symptoms, whereas only 12 of 18 patients in the HBOT-alone group had symptom scores of the same severity. Subjects with more refractory symptoms, such as tooth decay, chronically exposed mandibular bone, osteomyelitis, and nonhealing soft tissue wounds with superimposed infection, were deemed less likely to respond to HBOT alone and, hence, tended to receive more aggressive

treatment (HBOT and surgery). Similarly, these patients were also more predisposed to symptom relapse. In fact, 3 of 4 H&N subjects with post-HBOT symptom recurrence required the combined treatment of HBOT and surgery. Contrary to what we might have expected, only 1 of 4 H&N subjects with post-HBOT relapse had failed surgical management in the past. Hence, past response to surgery is not a reliable gauge of future HBOT success. It is also important to note that 4 of 21 H&N patients with improvement received HBOT within the last 12 months. Therefore, our inquiry into their symptom relapse and long-term HBOT response might have been temporally limited.

All 14 non-H&N subjects were treated with HBOT alone. Although a few patients in this group also had skin graft or wound revisions in the past, these surgical procedures were completed many months before initiating HBOT at UCLA and, therefore, not considered part of this treatment. In this non-H&N group, radiation cystitis and proctitis responded well to HBOT alone, although the number of patients with these symptoms in this study is limited. Similarly, Woo *et al.* (40) also found an overall favorable response of radiation proctitis to HBOT in 16 of 18 patients in their retrospective study. Symptoms recurred in 1 of 3 subjects with radiation proctitis, but the number of patients in these groups was too low for any definitive comparisons of long-term response or relapse. In contrast to proctitis, upper GI symptoms were more resistant to HBOT. Whereas 3 of 4 subjects with radiation proctitis in our study responded well to HBOT, only 1 of 14 with dysphagia or odynophagia showed some improvement on the same treatment. Though the low response rate of upper GI symptoms seems in stark contrast to the response rate of proctitis, the resistance of upper GI symptoms to treatment might be unfavorably compounded by the concurrent salivary gland problems that many of these patients also experienced from their past radiation therapy. Needless to say, salivary gland dysfunction after therapeutic radiation is a difficult, if not impossible, problem to reverse, and it is a factor in other complications, such as caries. Surprisingly, 10% of subjects in this symptom category improved, raising the question of whether patients with radiation-induced salivary gland dysfunction may be considered for HBOT. For selected H&N cancers, the advent of conformal radiation treatment allows the radiation oncologist to spare the contralateral parotid gland, thus decreasing the likelihood of more severe late salivary gland problems. Patients who have had bilateral salivary glands irradiated or have significant xerostomia deserve consideration for HBOT in the light of this finding. Unfortunately, the existing theoretical potential for tumor regrowth with HBOT (41) may limit its application as an early adjunct to the routine management of this patient group. With this consideration, HBOT may still be an appropriate treatment modality in patients who are deemed free of cancers.

Our study has shown that HBOT is a safe treatment associated with few serious side effects. Most complications were minor and transient, limited to the duration of the treatment course. Excluding accelerated cataract formation, patients experienced relief or complete resolution of auditory, eye, or epistaxis symptoms during HBOT course. No long-lasting residual side effects were reported among patients who encountered problems during HBOT. No complications necessitated any emergency procedures during or after the treatment course or altered the patient's HBOT. This is supported by a previous study (40).

The overall rate of relapse after HBOT for the whole cohort was low (22%). These patients received durable remission of their problematic symptoms, indicating the beneficial nature of HBOT. Patients with bladder symptoms (cystitis) and radiation proctitis were most likely to relapse, but the small number of patients ($n = 6$ and 3, respectively) does not permit us to reliably predict long-term response of HBOT. On the other hand, we did have a large number of subjects with osteoradionecrosis, and the findings of this study do support the use of HBOT in this group of patients, especially because they failed to respond to previous aggressive medical and surgical management. Our study supports other retrospective studies and case reports stating the potential benefits of HBOT in the management of radiation-induced late side effects (17–20, 22–28, 42).

The most common radiation-related symptoms that have been shown to improve on HBOT include cystitis, osteoradionecrosis, proctitis, and soft tissue wounds. Nonetheless, the lack of a prospective randomized control trial certainly speaks for the need to further investigate the true efficacy of HBOT (43, 44). Careful documentation of pre- and post-treatment subjective as well as objective evaluations by a multidisciplinary team in a prospective study will ensure the reliability of data analysis and provide validation of the effects of HBOT.

The retrospective nature of the present study means that we have to view our findings with caution. For example, relying on the patients' ability to recall symptoms that they experienced, as well as medical records, can introduce bias and the potential for inaccuracies in the effect of the treatment measured. However, the treating hyperbaric oxygen physician (M.L.) prospectively documented the progress of major symptoms on HBOT, allowing the comparison between the patient's questionnaire response and the physician's evaluation to improve accuracy of final data. Overall, we found a high degree of patients' responses concurring with the medical record (98%). This is primarily because radiation late side effects are severe and difficult to forget. Our questionnaire focused not only on the principal presenting symptoms described in Hyperbaric Unit medical records but also on other concurrent symptoms, enabling some subjective measurement of the differential efficacy of HBOT on many symptoms. Another criticism of the present study is that some late side effects may spontaneously improve over time without HBOT, and this was not controlled for in the present design of this study. Because we were unable to recruit all eligible patients, the selection bias among participating respondents may also confound the overall result. Despite this, we did accrue a relatively large cohort compared to most other studies in the literature (26,

28, 40), which enabled us to present useful observational data, especially in the H&N cohort.

CONCLUSIONS

Our retrospective study indicates that HBOT seems to be an efficacious treatment modality for many radiation-induced late side effects. Clinicians may consider using this treatment in patients determined not to have tumor recurrence. Refractory bone symptoms arising from radiation treatment of the head and neck are highly amenable to HBOT, although success tends to require the maintenance of concurrent medical treatment, such as antibiotics and pain control, during the HBOT course. Severely infected tissues or large wounds usually require the addition of surgical procedures to optimize HBOT success. Duration of response seems sustainable among patients with post-HBOT bone symptom improvement, even in those who eventually relapsed. Patients with protracted late side effects tended to be less likely to respond as well to HBOT, even when it was combined with more aggressive management such as surgery. One interesting incidental finding of this study was that a minority of patients with salivary gland dysfunction received some relief from HBOT.

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