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REVIEW ARTICLE

Hyperbaric oxygen therapy for chronic radiotherapy-related adverse effects: A clinically focused review

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Abstract

Radiotherapy is a cornerstone of modern oncologic care, yet its sequelae can significantly impair survivors' quality of life. Chronic radiation-induced conditions—including skin fibrosis, bone necrosis, radiation cystitis, and proctitis—pose substantial challenges for both patients and caregivers, particularly in the context of improving long-term cancer survival. Hyperbaric oxygen therapy, characterized by the promotion of angiogenesis, fibroblast activation, and tissue remodeling in hypoxic environments, has emerged as a potential adjunctive treatment for mitigating these late effects. Herein, the authors critically evaluate randomized trials, cohort studies, and real-world data while highlighting gaps in knowledge, including patient selection, optimal treatment protocols, and long-term outcomes. In addition, they discuss practical considerations and health system implications of the integration of hyperbaric oxygen therapy into survivorship care. The objective of this review is to provide clinicians with an evidence-informed framework to guide decision making in the multidisciplinary management of radiation-related late effects.

KEYWORDS
chronic adverse effects, hyperbaric oxygen therapy, radiotherapy, review, survivorship

INTRODUCTION

With an aging population and ongoing advances in oncology, the global number of individuals living after a cancer diagnosis continues to rise. In the United States alone, the number of cancer survivors is projected to exceed 22 million by 2030, a marked increase from 15.5 million in 2016.[1,2] This epidemiologic shift underscores the importance not merely to extend life but also to improve the quality of life within. Although clinical interest predominantly focuses on reducing acute morbidity, many survivors experience chronic, sometimes debilitating, complications from prior therapies.

Radiotherapy is a fundamental component of cancer care, and greater than 50% of individuals who are diagnosed with cancer receive at least one course of irradiation.[3,4] Although technological advances (such as superior diagnostic imaging, computed tomography-guided treatment planning, and intensity-modulated and image-guided radiotherapy) have improved precision and allowed for effective normal tissue sparing, chronic radiation-induced conditions remain a persistent issue in modern-day survivorship.[5] These late effects—manifesting months to years after treatment (i.e., with latency)—are poorly understood. Chronic inflammation, vascular injury, and hypoxia lead to (lymph-)edema, fibrosis, and necrosis, in turn giving rise to ulcers and fistulas, ultimately resulting in functional damage to the involved organs (e.g., skin and mucous membranes, bones and cartilage, nervous system, lungs, bladder, or rectum; Figure 1).[5,6] In serial organs (e.g., bowel or vessels), focal radiation exposure can impair the function of downstream sections. Although incidence varies with age, radiation dose, and anatomic site, an estimated 5%–10% of patients will eventually develop severe late effects after radiotherapy, the burden of which is underrecognized, underreported in clinical trials, and frequently underestimated by health care professionals in survivorship planning.[7,8] Individuals living with these sequelae often describe them as both physically and emotionally burdensome. As an example, individuals experiencing chronic radiation cystitis may face recurrent bleeding, pain, and loss of bladder control, limiting their ability to work, travel, or engage socially. Furthermore, associated symptoms can incite anxiety of tumor recurrence, negatively affecting quality of life. In qualitative interviews, survivors have reported unawareness that adverse effects could continue or emerge after the end of radiotherapy, in sharp contrast to the usually appropriate and individualized information on acute side effects.[9] Therefore, chronic radiation injuries can be regarded as a *silent aftermath* of cancer treatment—one that is poorly understood and inadequately addressed by current health care systems. These insights highlight an essential truth: surviving cancer is different from surviving cancer treatment.

Unfortunately, clinical options for managing these chronic radiotherapy-related side effects are limited. Supportive measures, such as anti-inflammatory drugs, antispasmodics, instillations, or even surgical interventions, offer symptom relief for some, but few are curative. The biologic background of radiation-induced late effects, characterized by hypoxia and fibrosis, makes them uniquely resistant to conventional therapies.[10]

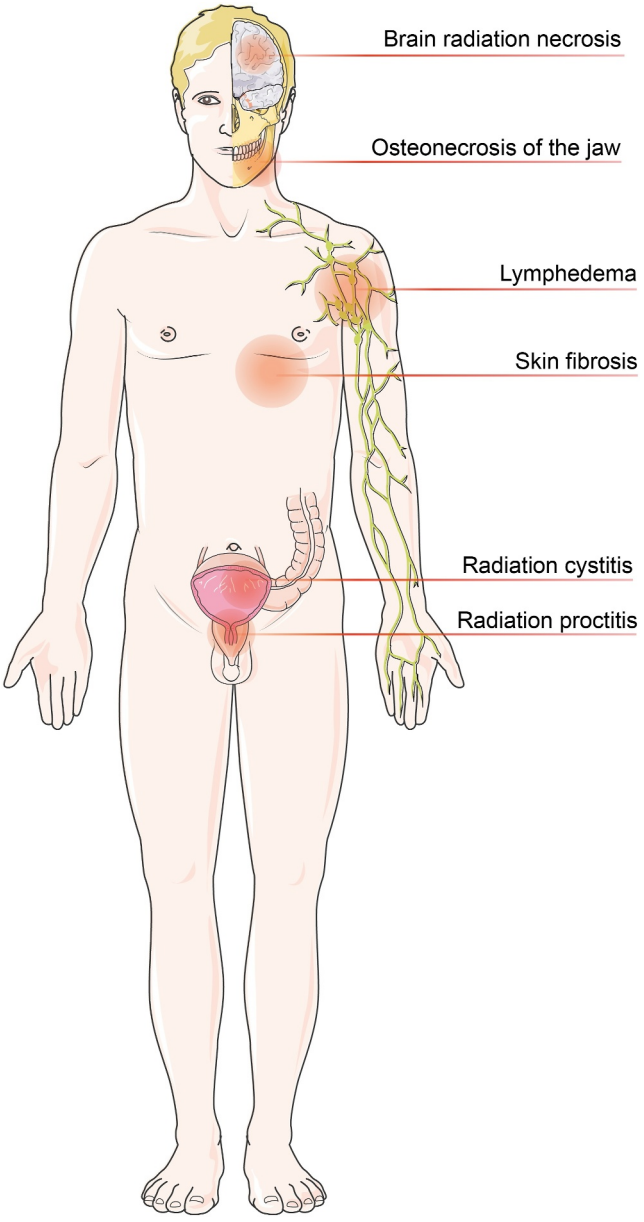

FIGURE 1 Common radiotherapy-related late effects in which hyperbaric oxygen therapy has been studied.

Hyperbaric oxygen therapy (HBOT) may hold the potential to bridge the critical gap in care caused by this discrepancy between illness-specific pathogenesis and available treatment options. In its early days, HBOT was mainly used to treat decompression illness in divers by counteracting the formation and dissemination of nitrogen bubbles in the bloodstream.[11] Currently, the 2017 European Consensus Conference on Hyperbaric Medicine recommends the use of HBOT for 22 distinct indications supported by either sufficiently strong or acceptable levels of evidence, of which six (27%) are radiotherapy-related.[12] Other and more common consensus-agreed recommendations include its use in the management of chronic, nonhealing wounds, diabetic foot ulcers, and surgical graft failure.[12] HBOT requires the delivery of medical grade O_2 (i.e., >99% oxygen purity) at an elevated atmospheric pressure of 1.9–6.0 atmospheres

absolute (ATA; most commonly in the range of 2.0–2.5 ATA) for an amount of time that is typically between 90 and 120 minutes per treatment session, usually applied daily, five times per week.[13] The number of sessions differs by indication, but treatment usually spans several weeks.

Over the past decades, the potential utility of this pathogenesis-centered approach has steadily gained attention in radiation oncology. Early observational reports suggested benefit in treating mandibular osteoradionecrosis (ORN), radiation cystitis, and proctitis.[14–16] Subsequent prospective and randomized trials have further shaped our understanding of where HBOT may or may not be helpful.[17,18]

To date, most clinicians remain unfamiliar with the mechanism, indications, and evidence base of HBOT to treat radiation-induced conditions. In addition, access disparities—geographic, financial, and logistical—compound barriers to care, particularly for structurally vulnerable populations. In this clinically oriented review, we aim to provide a practical and patient-centered framework for the use of HBOT in the management of chronic radiotherapy-related late effects, emphasizing actionable guidance for clinicians across different specialties. Where evidence is strong (randomized clinical trials), we recommend the integration of HBOT into clinical care pathways. Where data are limited (consensus guidelines, large retrospective studies, and expert recommendations), we aim to identify research priorities and clinical decision points to address this actionable need in current oncologic care.

PATHOPHYSIOLOGY OF CHRONIC RADIATION INJURY

In contrast to acute radiation injury, which is generally self-limiting shortly after completion of treatment, chronic radiation injury arises months to years after radiotherapy and is driven by a complex interplay of biologic mechanisms that vary across tissue types.[19] Central to these late effects is progressive vascular damage, characterized by endothelial dysfunction, capillary rarefaction, and subsequent compromised perfusion, ultimately promoting local tissue hypoxia and necrosis.[20,21] Chronic inflammation, often sustained by persistent oxidative stress and perpetually active (fibrogenetic) cytokine cascades, leads to fibroblast activation and excessive extracellular matrix deposition, culminating in fibrosis and impaired tissue regeneration.[22,23] These processes manifest differently, depending on the irradiated organ, yet all share common features of hypoxia, fibrosis, and altered immune homeostasis. Late effects can theoretically affect any organ system; individual sensitivity, however, varies.[24] Most commonly involved areas include the head and neck region, breast and chest wall, and pelvic organs, such as bladder and rectum. Yet this rather reflects anatomic regions frequently irradiated with curative intent (i.e., with sufficiently high radiation doses yielding tumor control in a large proportion of patients, but equally placing patients at risk of developing late effects).[25]

Mechanistically, HBOT provides an increased O_2 concentration in the blood (i.e., partial pressure) by creating a positive gradient, leading to an improved O_2 availability in hypoxic tissues, regardless of hemoglobin concentration.[26,27] Re-oxygenation, in turn, promotes angiogenesis, enhances fibroblast function, reduces tissue edema (through the vasoconstrictive effects of O_2), and modulates inflammatory responses by shifting macrophage phenotypes toward tissue-repairing profiles, thus counteracting many of the core pathophysiologic features of chronic radiation injury, ultimately exerting the observed benefits of HBOT in this context (Figure 2).[28,29] The properties of HBOT are unique in terms of being the only intervention capable of increasing the number of blood vessels in irradiated healthy tissues.[30,31]

PRINCIPLES AND DELIVERY OF HBOT

HBOT is performed in a sealed hyperbaric chamber, with a capacity of from one person (monoplace) up to 20 persons (multiplace; Figure 3)[32]. HBOT is usually performed in an outpatient setting, but some chambers can accommodate gurneys or hospital beds, for example, in the perioperative setting. In the United States, the Undersea & Hyperbaric Medical Society estimated that the number of hyperbaric treatment facilities was approximately 1300 in 2020 (i.e., one per 255,000 capita).[33] Only a minority of these, however, fulfill criteria to treat high-acuity patients.[34] By contrast, in Germany, only 15 certified facilities were identified as of 2025 (i.e., one per 5.6 million capita), reflecting more stringent certification standards, a narrower range of approved indications, and subsequent restrictive reimbursement policies compared with the United States.[35] Accurate numbers in low-income and middle-income countries are difficult to acquire, but availability seems limited to few tertiary centers. There is an increasing number of nonmedical facilities (e.g., medical spas) offering so-called *mild* HBOT, with O_2 concentrations <95% at pressures <1.5 ATA. Although regular HBOT indications are often advertised, these are not evidence-based nor physician-prescribed or supervised.[13]

HBOT is generally well tolerated, with a favorable safety profile (Table 1). Side effects are related to increased pressure or hyperoxia.[28,36] The probability of developing adverse reactions is higher with an increasing number of treatment sessions (usually >10) and pressures above 2.0 ATA.[37] One of the most common adverse events is minor middle ear barotrauma (2%–3%), which can present as difficulty with ear equalization, ear discomfort or pain, or even transient hearing loss.[28] The risk can be minimized by applying adequate compression rates and through good patient communication.[38–40] Importantly, a history of head and neck malignancy is a known risk factor for HBOT-related middle ear barotrauma.[28] Myopia, stemming from lenticular dysfunction, occurs with an incidence of 25%–100%, depending on its definition.[41] It is usually progressive throughout treatment (at a rate of approximately 0.25 diopters per week of HBOT) and fully reversible after discontinuation (although this can take up to 12 months).[42,43] Pulmonary barotrauma, with cough and inspiratory pain, seldomly giving rise to pneumothorax, is also

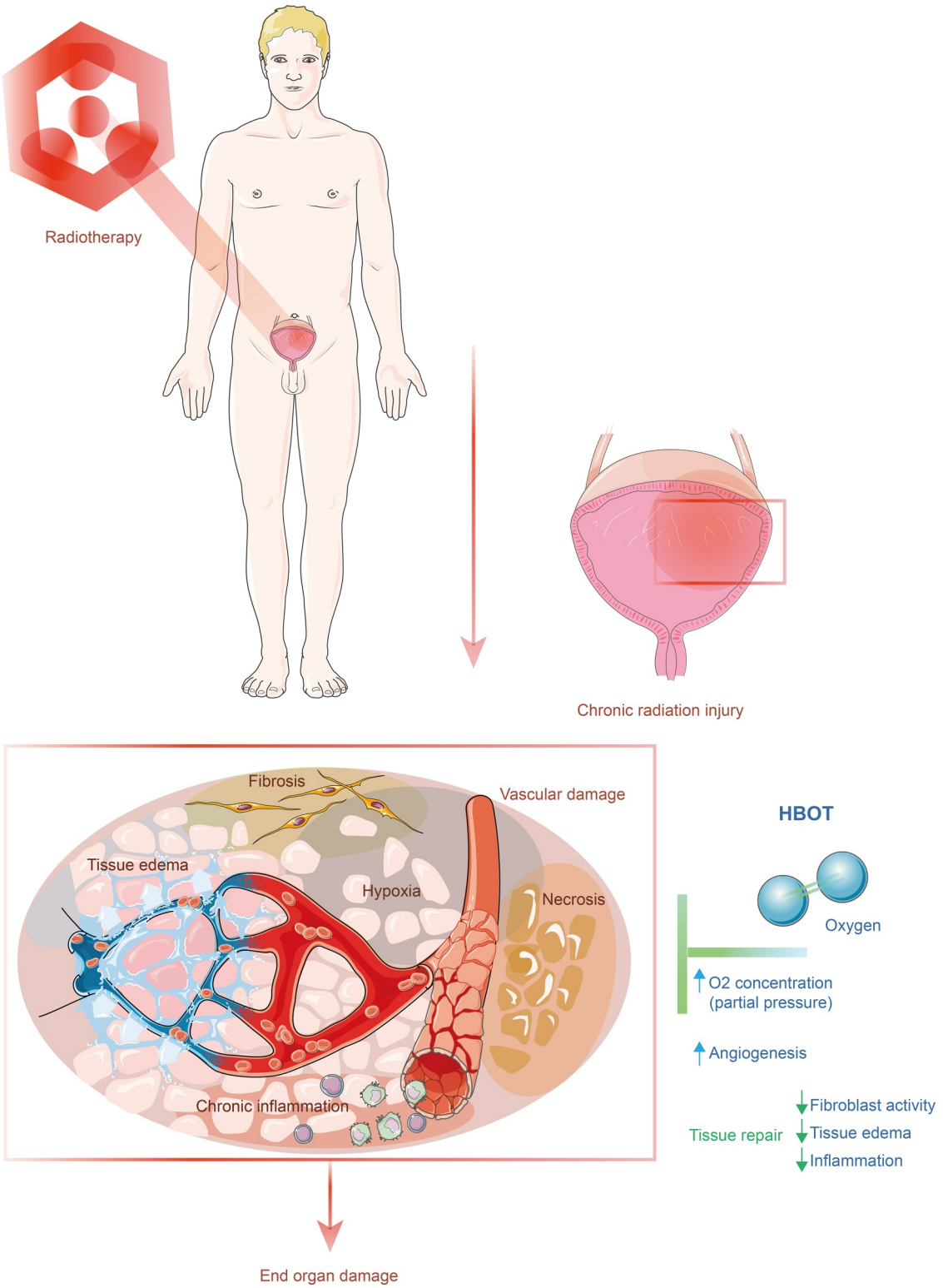

FIGURE 2 Pathophysiology of chronic radiation injury and hyperbaric oxygen therapy (HBOT).

possible but usually is seen in only patients with certain predispositions (e.g., history of asthma or chronic obstructive pulmonary disease).[28,30] Recent thoracic imaging should be reviewed to appropriately balance risks and benefits when considering HBOT. Oxygen toxicity most commonly affects the central nervous system, rarely in the form of a seizure, with an estimated incidence of one per 2000–3000 treatments, primarily depending on the oxygen partial pressure.[44] Claustrophobia, also observed within multiplace chambers, might require relaxation exercises, behavioral therapy, or light sedation. Other potential side effects that have been reported, albeit

FIGURE 3 (*Left*) Monoplace and (*middle*, *right*) multiplace hyperbaric oxygen chambers (reproduced with permission from Pawlik et al., 2024[32]; licensed under a Creative Commons Attribution 4.0 International License).

TABLE 1 Potential side effects associated with hyperbaric oxygen therapy.

Side effect	Incidence
Myopia (usually transient)	25%–100%
Middle ear barotrauma (difficulty with ear equalization, ear discomfort or pain, transient hearing loss)	2%–3%
Pulmonary barotrauma (cough and inspiratory pain, rarely pneumothorax)	Rare
Oxygen toxicity (e.g., manifesting as seizure)	1 per 2000–3000 treatments
Claustrophobia	Rare
Hypoglycemia	Rare
Hypertension	Rare
Acute pulmonary edema	Rare

with very low incidences (i.e., <0.5%), include hypoglycemia, hypertension, and acute pulmonary edema.[28,36] Possible side effects and management strategies should be discussed before HBOT initiation, and patients should be monitored continuously throughout treatment.

Absolute contraindications are limited and include untreated pneumothorax and intraocular gas for nonemergent HBOT indications.[45] Relative contraindications encompass conditions such as asthma or chronic obstructive pulmonary disease and severe claustrophobia. In patients who have implantable devices, compatibility should be verified with the manufacturer and disabling considered if clinically acceptable.[45] Certain chemotherapeutic agents (e.g., bleomycin, doxorubicin) and other drugs should not be combined with HBOT because of potential synergistic toxicity, which is especially relevant in the oncologic setting (Table 2).[45–47] There is a lack of experience when combining newer antineoplastic agents (e.g., immunotherapies, targeted therapies) with HBOT. In general, close patient monitoring for signs of increased side effects is warranted in this patient population.

EVIDENCE BY INDICATION

Radiation-induced skin fibrosis and lymphedema

Late effects after breast or chest wall irradiation can manifest as local fibrosis and edema, presenting as pain, movement restriction, and an impaired cosmetic outcome, significantly affecting quality of life (Table 3).[16,18,48–52] Despite recent technical advances with modern radiotherapy techniques, these adverse events reportedly still occur in a relevant 16% of patients.[53] A 2023 systematic review (nine studies; 1308 patients) reported various reductions in fibrosis, lymphedema, pain, shoulder immobility, and skin problems after 20–60 HBOT sessions of 80–90 minutes each at 2.4–2.5 ATA.[54] Although seven of those studies were prospective, the majority had inadequate methodology with a substantial risk of bias. Of note, a single retrospective study (with a median follow-up after HBOT of only 3 months) accounted for greater than three quarters of the total pooled sample size, restricting generalizability.[55]

To further evaluate the role of HBOT for local late effects in women who received adjuvant radiotherapy for breast cancer, the Dutch HONEY trial (The Effect of Hyperbaric Oxygen Therapy on Breast Cancer Patients with Late Radiation Toxicity; ClinicalTrials.gov identifier NCT04193722) randomly assigned 189 patients who had patient-reported, moderate-to-severe, late, local toxic effects (pain in combination with lymphedema, fibrosis, or movement restriction) >12 months after adjuvant radiotherapy (2:1) to receive 30–40 HBOT sessions (over a standard period of 6–8 weeks) or standard of care (consisting of physiotherapy, edema therapy, psychotherapy, analgesics).[48,56] Interestingly, the authors used a trial-within-cohorts design, in which eligible participants of an observational cohort are randomized: those allocated to the experimental arm may decline treatment and cross over to the control arm, whereas those randomized to the control arm continue to receive standard of care within the

TABLE 2 Chemotherapeutic agents and other drugs in which caution is warranted when considering hyperbaric oxygen therapy.

Agent/drug	Indication	Risk	Recommendation
Bleomycin	Squamous cell carcinoma, lymphoma, malignant pleural effusion, germ cell tumor …	Pulmonary toxicity	HBOT if no evident pulmonary toxicity, 3–4 months distance
Doxorubicin	Lymphoma, breast cancer, sarcoma …	Cardiac toxicity	3 days' distance to HBOT
Cisplatin	Head and neck, bladder, gynecologic …	Nephrotoxicity and ototoxicity, delayed wound healing (reduced HBOT effectiveness)	Not parallel to HBOT, especially in wound-healing indications
Disulfiram	Alcohol dependence	Oxygen toxicity	Discontinue before HBOT
Mafenide	antibiotic	Acidosis	Discontinue before HBOT

Abbreviation: HBOT, hyperbaric oxygen therapy.

TABLE 3 Summary of the most important trials.

Trial (reference)	Year	Indication	Design	No.	Intervention	Primary outcome
HONEY (Mink van der Molen 2024[48])	2024	Patient-reported moderate or severe *breast, chest wall, and/or shoulder pain* in combination with *mild, moderate, or severe edema, fibrosis, or movement restriction* >12 months after breast irradiation	Pragmatic, two-arm; randomized trial within cohort	125	30–40 HBOT sessions over a period of 6–8 consecutive weeks, 120 minutes per session, 2.5 ATA	HBOT not effective for reducing pain but effective for reducing fibrosis; a significant reduction in pain and fibrosis in the subgroup of women who completed HBOT
HOPON (Shaw 2019[18])	2019	Patients requiring *dental extractions or implant placement in the mandible* with prior radiotherapy >50 Gy	Randomized, controlled, phase 3 trial	100	30 HBOT sessions, for 80–90 minutes, 2.4 ATA	Incidence of mandibular ORN at 6 months no different, patients in the HBOT arm had fewer acute symptoms but no significant differences in late pain or quality of life
DAHANCA-21 and NWHHT2009-1 (Forner 2022[49])	2022	Patients who have *mandibular ORN* with indication for surgical treatment	Randomized trial (both)	65	Surgical removal of necrotic mandibular bone + 30 preoperative and 10 postoperative HBOT sessions, 90 minutes per session, 2.4 ATA	HBOT did not significantly improve the healing outcome of ORN compared with standard care (70% vs. 51%), large type II error
RICH-ART (Oscarsson 2025[50])	2025	Patients with chronic *radiation-induced cystitis* and an EPIC urology score <80, having completed pelvic radiotherapy at least 6 months earlier	Randomized, controlled, phase 2–3 trial	87	30–40 HBOT sessions, for 80–90 minutes daily, 2.4–2.5 ATA	Long-term effects of HBOT in the treatment of chronic radiation-induced cystitis, with sustained symptom relief over 5 years
HORTIS-IV (Clarke 2008[16])	2007	Refractory *radiation proctitis*	Randomized, sham-controlled, double-blind, crossover trial	120	30–40 HBOT sessions, for 90 minutes daily, 2.0 ATA	HBOT significantly improved the healing responses, generating an absolute risk reduction of 32% ($n = 3$ needed to treat)
HOT2 (Glover 2016[17])	2016	*Chronic bowel dysfunction* >12 months after radiotherapy for pelvic malignancies, persisting despite >3 months of optimal medical therapy	Randomized, sham-controlled, double-blind, phase 3 trial	84	40 HBOT sessions, for 90 minutes daily, 2.4 ATA	No evidence that patients benefit from HBOT

Abbreviations: ATA, atmospheres absolute; EPIC, Expanded Prostate Index Composite; Gy, grays; HBOT, hyperbaric oxygen therapy; ORN, osteoradionecrosis.

observational cohort without being informed about their participation in a randomized trial.[57] This emerging design facilitates patient accrual because it prevents patients in the control arm from receiving the intervention (i.e., HBOT) off-trial. Of 125 participants who were offered HBOT, three quarters declined or withdrew consent after fewer than seven sessions, citing the high logistical burden of HBOT treatment as the main reason (77%).[48] Following intention-to-treat principles, the primary end point (patient-reported breast, chest wall,

or shoulder pain 6 months after randomization) was not met. Because many participants in the HBOT arm declined or discontinued treatment early, the authors performed an exploratory assumption-based *complier average causal effect* analysis to estimate outcomes among those who would have adhered to HBOT. In that analysis, patients who were actually receiving HBOT ($n = 31$) were compared with those in the control group who would have completed HBOT if offered ($n = 13$; this was based on the observed proportion of compliers in the HBOT-invited arm combined with the proportion of patients with moderate-to-severe pain in patients declining HBOT). In that trial, there was a significant effect on moderate-to-severe pain at follow-up in the HBOT group (32 vs. 75%; adjusted odds ratio [OR], 0.34; 95% confidence interval [CI]; 0.15–0.80; $p = .01$). The rates of moderate or severe, clinician-assessed (unblinded) fibrosis (per intention to treat) were 33% and 51% in the intervention and control arms, respectively (OR, 0.36; 95% CI, 0.15–0.81; $p = .02$). Quality of life was similar between groups. Adverse events were as expected, with fatigue (97%) and transient myopia (87%) occurring most frequently and middle ear barotrauma reported in 13% of patients undergoing HBOT. Of note, eight of 13 patients who had prior chemotherapy-induced peripheral neuropathy reported improvements 3 months after HBOT, a finding previously described in animal models.[58] Lymphedema at baseline was present in only 22% of patients and did not show any improvement, regardless of the type of analysis performed.

Although provocative, assumption-based analyses such as in the HONEY trial can only be treated as hypothesis-generating. Overall, the trial demonstrated that HBOT may not be acceptable to patients, as evidenced by attrition, which likely affected the primary analysis. Moreover, the long-term durability of HBOT beyond the relatively short median follow-up of 8 months remains unclear. Additional limitations include the unblinded trial design (reporting bias) and a general lack of improvement in patient-reported outcomes. The HONEY trial does hint at some meaningful benefits for carefully selected breast cancer survivors with refractory late effects, but its time-consuming and resource-intensive nature underscores the importance of shared decision making. Further large-scale studies with innovated delivery and shorter time courses as well as longer follow-up are needed to clarify optimal patient selection, timing, and cost effectiveness in this population. Although the small subset of patients with lymphedema in the HONEY trial had no improvement, four of seven studies that were included in a meta-analysis on HBOT for symptomatic late effects after breast cancer radiotherapy (280 patients) reported a significant reduction in edema.[54] Nevertheless, the absence of consistent reporting on axillary treatment and radiotherapy techniques limits the interpretability of these results because variations in axillary management represent major determinants of lymphedema development and response to HBOT.

Osteoradionecrosis of the jaw

ORN of the jaw is a serious late complication of head and neck radiotherapy, typically presenting with exposed, nonhealing bone, pain, and occasionally pathologic fractures or cutaneous fistulae, and is associated with substantial impairment of quality of life.[52] By using modern radiotherapy techniques, the estimated incidence of ORN is approximately 5%–10%, and risk factors include mandibular radiation dose, poor periodontal status, as well as alcohol consumption.[59] The prophylactic use of HBOT in the perioperative setting for dental implants after radiotherapy has been summarized in a Cochrane review.[60] Two controlled trials (100 patients; antibiotic prophylaxis as a comparator) had conflicting results and were classified as very-low-certainty evidence, preventing current recommendation.[61,62] The randomized controlled phase 3 HOPON trial (Hyperbaric Oxygen for the Prevention of Osteoradionecrosis; European Clinical Trials Database [EudraCT] identifier 2007-006225-27) recruited patients requiring dental extractions or implant placement in a previously radiation-exposed mandible (>50 grays).[18] The intervention consisted of standardized chlorhexidine mouthwash and antibiotics combined with HBOT (20 preoperative and 10 postoperative sessions of 80–90 minutes at 2.4 ATA) or HBOT alone. At 6 months, blinded assessment indicated 6% ORN development in both groups (OR, 1.13; 95% CI, 0.14–8.92; $p = 1.00$) and the trial was stopped at interim analysis (65% of target accrual) because of this lower-than-expected number of events. Acute (unblinded) patient-reported symptoms, such as pain, swelling, and bleeding, were less frequent in the HBOT arm, and these patients reported improved mouth opening and eating in the first 7 postoperative days. Differences in outcome between dental extractions or implant placement have not been reported. The high drop-out rate (citing the logistical demands of HBOT as the main reason) and the unexpectedly low number of events, resulting in an underpowered trial, do not justify a general recommendation for HBOT in this context, which is reflected by the current Multinational Association for Supportive Care in Cancer guideline for ORN.[63]

In patients who have ORN of the jaw requiring surgical intervention, perioperative HBOT has been investigated as an adjunct to resection. A randomized, double-blind, placebo-controlled trial from 2004 recruited patients with mild-to-moderate mandibular ORN (i.e., no fracture or bony reabsorption to the inferior border) and assigned them to 30 preoperative sessions and an additional 10 postoperative sessions (in those undergoing surgery) of 100% (HBOT arm) or 9% (control arm) oxygen for 90 minutes each at 2.4 ATA.[64] The placebo arm approximated ambient air (i.e., 21% oxygen) at 1.0 ATA. After the second interim analysis (31% of target enrolled), the trial was closed early because of potentially worse recovery rates in the experimental arm: at 1 year, the recovery rate was 19% versus 32% for the HBOT and control arms, respectively (relative risk, 0.60; 95% CI, 0.25–1.41; $p = .23$). Pain relief was similar between both groups. Note that not all patients underwent surgery, which is considered standard of care today. Furthermore, concerns were raised regarding ORN grading and lack of compliance with standard HBOT guidelines.[65]

The effects of HBOT for patients with severe overt ORN remained unanswered. This was partially addressed by a pooled analysis of two randomized trials (DAHANCA-21 and NWHHT2009-

1; EudraCT identifiers 2007-007842-36 and 2008-001972-55, respectively) recruiting patients with ORN and indication for surgical treatment.[49] By using the same HBOT regimen as the previous trial, the results indicated 70% versus 51% ORN healing at 12 months in an unblinded assessment (OR, 2.2; 95% CI, 0.7–7.0; $p = .13$). Although numerical differences were observed, these did not reach statistical significance because the trial was again markedly underpowered, with only 41% of the target sample accrued and a relevant 33% dropout rate (which had prompted the pooling of results in the first place). Interestingly, the HBOT group also exhibited numerically improved xerostomia and dysphagia, both of which are additional late effects of radiotherapy in the head and neck region that can have a major effect on quality of life in survivors. A meta-analysis of the DAHANCA-21 and NWHHT2009-1 trials, together with an earlier study that included all grades of ORN (104 additional patients), demonstrated that HBOT was associated with a higher likelihood of improvement or resolution of bone necrosis (relative risk, 1.44; 95% CI, 1.19–1.75; I^2 [heterogeneity] = 0%).[25,66] For the end point of patient-reported pain (157 patients), the same meta-analysis reported slight improvements with HBOT at 1 year (mean difference, −10.72 points; 95% CI, −18.97, −2.47 points; I^2 [heterogeneity] = 28%), yet this included HBOT both as a preventive and as a therapeutic strategy.[18,25,49]

In summary, the general prophylactic use of HBOT is not recommended in this context. For the treatment of mandibular ORN, careful patient selection, risk–benefit discussion, and integration into multimodal strategies (i.e., combination with surgical debridement or resection) remain key to optimizing outcomes. Evidence for HBOT in the context of ORN of other anatomic locations is currently limited, and no randomized trials were identified.

Radiation cystitis

Radiation cystitis is a challenging late complication after pelvic radiotherapy for malignancies such as bladder, prostate, cervical, or rectal cancer, manifesting primarily as persistent hematuria (often referred to as *hemorrhagic* cystitis), dysuria, and frequent urination (caused by a reduced bladder volume). Symptoms typically emerge 2 years after primary treatment, and the risk increases significantly with radiation doses >60 grays, which are commonly required in these tumor entities.[67,68] More recently, genetic predispositions have been described.[69]

This late effect, which currently affects an estimated 5%–15% of patients, is expected to become increasingly important in the coming years.[70] In prostate cancer in particular—the most frequent cancer diagnosis among men in most Western countries—ongoing improvements in survival are likely to result in a substantial rise in the number of patients experiencing radiation cystitis. The exploration of intensified radiotherapeutic approaches like ultrahypofractionation bears the risk of increased acute genitourinary toxicity, which is a consistent risk factor for developing late side effects and impaired quality of life.[71–74] In patients with refractory symptoms despite standard measures such as bladder irrigation, intravesical coagulation, or instillation (e.g., with hyaluronic acid), early retrospective and nonrandomized reports indicated a reduction of symptoms with HBOT.[75–77] The RICH-ART trial (Radiation-Induced Cystitis Treated with Hyperbaric Oxygen: A Randomized Controlled Trial; ClinicalTrials.gov identifier NCT01659723; EudraCT identifier 2012-001381-15) was a Scandinavian phase 2–3 trial that included patients with a history of pelvic radiotherapy (>6 months prior) and significant patient-reported bladder symptoms (defined as a score <80 in the urinary domain of the Expanded Prostate Index Composite [EPIC], a dedicated questionnaire with urinary, bowel, sexual, and hormonal domains).[78] HBOT consisted of 30–40 sessions for 80–90 minutes at 2.4–2.5 ATA each, and the standard of care had no restrictions for other medications or interventions (not specified further). Eighty-seven patients (of these, two thirds had prostate cancer) were randomized; and the primary end point, the difference in change in patient-perceived urinary symptoms 6–8 months later, was met (17.8-point vs. 7.7-point EPIC score improvement in the HBOT and control group, respectively; mean difference, −10.1 points; 95% CI, −18.1, −2.2; $p = .013$). The number needed to treat was three (95% CI, 2–5).[25] The EPIC bowel scores also improved more markedly in the HBOT group (13.2 vs. 4.9 points, respectively; mean difference, −8.3 points; 95% CI, −15.5, −1.2; $p = .024$), illustrating that HBOT also positively impacts late bowel effects (i.e., radiation proctitis), which often coincide with radiation cystitis because of anatomic proximity. Although patients in the control group also experienced significant improvements in both urinary and bowel domains of EPIC throughout initial follow-up, the differences were consistently more pronounced with HBOT. Compliance was good (low attrition), and treatment was considered safe, with transient grade 1–2 adverse events (related to sight and hearing) reported in 41% of patients. Interestingly, the authors reported macroscopic changes of the urothelium upon cystoscopy (atrophy, telangiectasia, hematuria, bladder capacity, the presence of necrosis or ulcerations) during follow-up (according to a blinded assessment). In the recently published, long-term follow-up (5 years), the authors report additional details: patients assigned to the control group were allowed to cross over and receive HBOT (only one patient declined).[51] In the total group, the observed improvement in both the urinary and bowel EPIC domains remained stable over time. Those who had recurring symptoms after >12 months (13%) received an additional 20–30 HBOT sessions. Although subsequent results are not reported separately, it is of interest that the majority of these patients initially had received only 30 sessions of HBOT (i.e., the lower boundary of the intervention), prompting the hypothesis of a dose–response relationship requiring further investigation.

In summary, HBOT can be offered to patients with late radiation-induced cystitis and should be preferred over urinary diversion, bladder embolization, or cystectomy, both of which potentially could lead to further deterioration of quality of life. Early referral and initiation seem beneficial because there are signs of improved efficacy with short intervals (i.e., within 6 months) between hematuria onset and HBOT.[15,79] Of note, HBOT is approved by the US Food and

Drug Administration in patients with radiation-related hemorrhagic cystitis, but not in those with chemotherapy-related hemorrhagic cystitis, because evidence in this setting is currently limited.[80–82]

Radiation proctitis

Radiation proctitis is a frequent and often debilitating late effect after pelvic radiotherapy, manifesting as rectal bleeding (sometimes requiring transfusion), pain, urgency, and tenesmus, again severely impairing quality of life.[83] Diagnosis is confirmed through endoscopy, revealing edematous, friable mucosa with telangiectasia and sometimes ulceration. The estimated incidence of chronic, moderate-or-severe gastrointestinal symptoms is approximately one quarter, although rates of up to one third have been reported, potentially reflecting insufficient long-term follow-up and frequent underrecognition.[84,85]

Two key randomized controlled trials have investigated HBOT for chronic radiation proctitis: the HORTIS-IV trial (Hyperbaric Oxygen Treatment for Chronic Radiation Tissue Injury Study) and the HOT2 trial (Randomized Double-Blind Controlled Phase 3 Trial of Hyperbaric Oxygen Therapy in Patients Suffering Long-Term Adverse Effects of Radiotherapy for Pelvic Cancer; International Standard Randomized Controlled Trial Numbers ISRCTN85456814 and ISRCTN86894066, respectively).[17,86] Interestingly, these trials yielded differing results, highlighting both promise and limitations of HBOT in this setting. The 2008 HORTIS-IV trial randomized patients with (medically and endoscopically) refractory radiation proctitis to HBOT at 2.0 ATA or air (i.e., 21% oxygen) at 1.1 ATA with subsequent cross-over to HBOT after primary outcome assessment at 3 months (i.e., the double-blind Late Effects on Normal Tissues—Subjective, Objective, Management, and Analytic, an instrument considering both clinician-reported and patient-reported outcomes in addition to objective measures).[86] Of 120 evaluable patients, mean scores improved in both groups after randomization; however, the effect was significantly greater in the HBOT group (5.00 vs. 2.61 points; $p = .002$). This difference disappeared after cross-over, and further improvements were noted in both groups throughout follow-up (consistently up to 5 years), along with marked improvements in bowel-specific quality of life (including fecal incontinence and pain). In 2016, the HOT2 trial results were published, randomly assigning 84 patients who had persisting gastrointestinal symptoms at least 12 months after initial diagnosis and had received 3 months of optimal medical therapy (2:1) to 40 sessions of HBOT (2.4 ATA) or air (1.3 ATA).[17] At 12 months, this trial failed to detect a clinically relevant benefit of HBOT in blinded, patient-reported outcomes or rectal bleeding. The reason for this discrepancy is thought to be related to patient selection (overall milder symptoms and longer intervals after radiotherapy) and choice of the end point (an unvalidated instrument) in HOT2.

Overall, HOT2 highlights limitations of HBOT and the need for more precise patient selection and robust outcome measures in future trials, aiming to identify which subgroups derive meaningful benefit from HBOT. Based on a large body of equivocal, retrospective evidence in addition to the well designed RICH-ART and HORTIS-IV trials, the Multinational Association for Supportive Care in Cancer guideline currently recommends the use of HBOT as an effective way to treat radiation-induced proctitis in patients with pelvic malignancies.[87]

Other

The incidence of cerebral radiation necrosis is rising, after an increasing adoption of stereotactic radiotherapy techniques for limited brain metastases.[88] First-line treatment in symptomatic patients usually includes corticosteroids for 3–6 weeks; however, this might impair survival, particularly in the growing subset of patients who receive immunotherapy.[89,90] Therefore, there is a need for effective alternatives.[91] Pathophysiologically, radiation-induced brain necrosis stems from endothelial injury and subsequent vascular alterations, thus postulating a potential role for HBOT in this context. Evidence is currently limited to uncontrolled, retrospective series with small sample sizes, however, preventing a clear recommendation.[92,93] The same holds true for radiation-induced damage of peripheral nerves (e.g., brachial plexopathy).[94]

Xerostomia is related to the radiation dose delivered to the major salivary glands. A small trial ($n = 21$) of patients undergoing HBOT for ORN of the jaw observed improvements in xerostomia, swallowing-related problems, and taste.[95] Another small randomized trial ($n = 19$) investigated the effects of HBOT administered shortly after radiotherapy for head and neck cancer, demonstrating improved quality-of-life scores for swallowing, sticky saliva, xerostomia, and mouth pain.[96] In addition, the above-mentioned DAHANCA-21 and NWHHT2009-1 trials also reported improvements in xerostomia.[49,97] Thus although a positive effect of HBOT on xerostomia appears reasonable, robust prospective evidence is currently lacking.[98]

More uncommon indications, such as laryngeal and cutaneous radiation necrosis, have not been investigated in isolated trials, but indirect evidence for potential efficacy of HBOT comes from large series that included heterogeneous patient populations.[24,99] A systematic review of HBOT trials for late effects after radiotherapy for gynecologic malignancies reported improvement in patients who had wound complications (necrosis, fistula, ulceration).[100] The majority of included trials, however, were of a retrospective nature. Interestingly, one trial reported sustained benefits in ulceration, dyspareunia, and pain in the majority of responders at 3-month follow-up.[101] High-level evidence could not be identified for any of these late effects.

GAPS, CONTROVERSIES, AND FUTURE DIRECTIONS

Although the number of trials on HBOT for late radiation-related effects is steadily rising, increased accumulation of high-level evidence is disproportionally slow (Figure 4).[25] The current landscape of data is heterogeneous, with significant variability in patient populations, definitions of treated indications, and outcome measures,

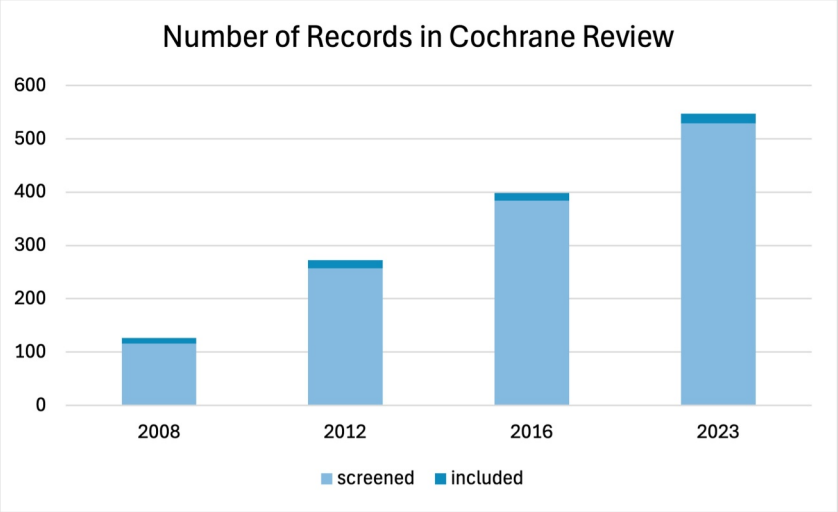

FIGURE 4 Overall number of trials on hyperbaric oxygen therapy for late radiation-induced side effects according to the Cochrane Collaboration. Only a small fraction of publications generates high-level evidence (Lin et al., 2023[25]).

limiting generalizability in many cases. The majority of studies suffer from methodological limitations, such as small sample sizes (mostly because of slow accrual and high drop-out rates) and lack of sham control (e.g., breathing air at a lower pressure) or blinding to eliminate systematic biases. A sham-controlled design in particular is often criticized because of ethical concerns of exposing a group of patients to an ineffective yet highly time-consuming intervention.[102] In some trials (e.g., HORTIS-IV), however, the sham effect resulted in a significant improvement of symptoms.[86] To overcome these limitations, offering cross-over after assessment of the primary end point seems justified. In addition, health care providers might be reluctant to enroll their patients, who sometimes experience debilitating symptoms, in a randomized trial investigating an intervention that is readily available off-trial. This could be one of the reasons why the HORTIS-III trial (investigating radiation cystitis; International Standard Randomized Controlled Trial Number ISRCTN19501634) closed early or why other trials were underpowered (e.g., HOPON, DAHANCA-21, and NWHHT2009-1).[18,49,103] Therefore, the trial-within-cohorts design (e.g., as in the HONEY trial) may provide a solution because patients in the control arm receive standard-of-care treatment and are not informed about the experimental arm.[56]

In general, HBOT protocols vary widely in terms of pressure, duration, and number of sessions, underscoring the need for standardization based on a better understanding of pathophysiology. In addition, future trials require rigorous, structured follow-up to adequately assess the long-term durability of potential benefits. Research priorities should include the identification of predictive biomarkers, the incorporation of advanced imaging techniques to quantify tissue response, and a systematic assessment of patient-reported outcomes to more adequately capture therapeutic impact.

Financial disparities and access might be an additional barrier to HBOT; however, as more intensive (e.g., surgical) interventions may be avoided and other medical management requirements discontinued, HBOT has been proven to be cost effective in some contexts.[104,105] HBOT does remain unevenly available across regions and health care systems; the need for specialized equipment, trained personnel, and multiple treatment sessions poses logistical and financial barriers that disproportionately affect patients in rural areas and those treated in nontertiary centers. In many health care settings, HBOT is not routinely reimbursed or remains restricted to very specific indications only, further limiting accessibility. Consequently, patients with similar clinical needs may experience markedly different opportunities for symptom relief and tissue recovery based solely on geographic location or institutional resources, underscoring an important inequity in supportive oncologic care.

PRACTICAL CONSIDERATIONS FOR CLINICIANS

After technical improvements in radiotherapy planning and delivery, the overall incidence of late toxicity might be considered to be decreasing. However, with consequently intensified treatment schemes as well as an increasing number of cancer survivors and latency after treatment completion, health care providers must stay vigilant. Some late effects might mimic local tumor recurrence, which should always be ruled out before starting survivorship care. Importantly, if one late effect is diagnosed, clinicians should be alert for additional radiation-induced soft tissue lesions, which occur in more than one third of patients and also potentially could benefit from HBOT (e.g., cystitis and proctitis).[50,106] In clinical practice, HBOT should be considered as part of the multidisciplinary approach to managing selected late radiation-induced toxicities. Strongest evidence is currently available for mandibular ORN (as a perioperative adjunctive modality to resective surgery) and for radiation cystitis and proctitis, in which HBOT has been shown to facilitate healing, to

improve quality of life by reducing symptom burden, and, in some patients, to obviate the need for more invasive interventions. Early referral is encouraged because late postradiogenic tissue changes underlie progressive fibroproliferative processes, with maximal benefit if HBOT is initiated before a certain threshold (i.e., before irreversible tissue damage occurs). Chong et al. observed improved outcomes if HBOT was initiated within 6 months of hematuria onset in radiation-induced hemorrhagic cystitis.[15] Clinicians should counsel patients that clinical improvements may be gradual, often becoming apparent only 2–3 months after HBOT completion, reflecting the delayed but progressive nature of tissue repair. Response might be faster with other (local) therapies; however, the effects of HBOT are considered to be more durable.[107] Side effects—such as ear barotrauma, myopia, or fatigue—are rare and generally mild but consistent across studies and typically resolve after treatment completion. A structured decision-making framework should include clear referral pathways, integration into survivorship or follow-up clinics, and interdisciplinary collaboration with radiation oncologists, wound care specialists, and hyperbaric medicine teams. Careful risk–benefit assessment considering comorbidities, patient preferences, and treatment goals, is essential to ensure the appropriate use of HBOT for late effects of radiotherapy.

CONCLUSION

HBOT is a unique intervention in the context of late radiation-induced effects because it is the only intervention known to provide symptom relief through disease modification. It holds promise as a supportive treatment for selected individuals and tissues, particularly for patients in whom conventional interventions offer limited benefit. Individualized and multidisciplinary clinical consideration based on patient characteristics, symptom burden, and available alternatives is a key factor in optimizing success. To clarify the therapeutic role of HBOT across expanding indications, rigorous, well designed studies are essential—ideally tailored to specific toxicity profiles and incorporating standardized treatment protocols and robust patient-centered outcome measures. In the interim, clinicians should engage patients in shared decision making that reflects current evidence, local expertise, and the practical availability of HBOT services in a timely manner.

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