EDITORIAL COMMENTARY

Challenges threaten, opportunity awaits hyperbaric medicine and the head and neck cancer patient

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ABSTRACT

Over the past four decades, hyperbaric oxygen (HBO_2) therapy has played a prominent role in both the prevention and treatment of mandibular osteoradionecrosis (ORN). It has done so on the strength of laboratory observations and clinical reports, yet only limited efficacy data. This dual role has come under increasing scrutiny in the modern radiotherapy (RT) and surgical eras. The ability to spare healthy "non-target" tissue has markedly improved since the two-dimensional planning and delivery techniques in use when HBO_2's prophylactic value was first demonstrated. A recent study failed to identify this same benefit in patients who received high-precision imaging and conformal RT. HBO_2 therapy is under challenge as preferred treatment for early stage ORN. A recently introduced "fibroatrophic" mechanism contrasts with the hypovascular-hypocellular-hypoxic injury pattern that formed the basis for HBO_2's therapeutic use. This alternative pathophysiologic state appears to benefit from an oral antioxidant medication regimen. The continuing necessity of HBO_2 in support of mandibular reconstruction for advanced ORN is in question. Microsurgery-based vascularized bone flaps increasingly represent standard care, invariably in the absence of perioperative HBO_2. Renewed interest in hyperbaric oxygen as a radiation sensitizer offers some promise. Hypoxia remains a critical radio-resistant factor in many solid tumors. Malignant gliomas have been a primary focus of several small studies, with resulting improvements in local control and median survival. Hyperbaric radiation sensitization has recently addressed oropharyngeal cancer. Preliminary data indicates that addition of HBO_2 to chemo-radiation standard of care is technically feasible, well tolerated and safe. A Phase II efficacy trial will investigate the potential for of HBO_2 to improve progression-free and relapse-free survival in newly diagnosed locally advanced head and neck cancers. What follows is a review and summary of relevant peer-reviewed literature. ∎

KEYWORDS: mandibular osteoradionecrosis; head and neck cancer; complications; osteoradionecrosis prevention

Prevention of mandibular osteoradionecrosis

Acute complications of head and neck cancer treatment occur during or shortly after radiotherapy (RT), are usually benign, invariably self-limiting and commonly managed by brief treatment interruptions. Late complications take many months to several years to manifest. In recent years, there has been something of a blurring of the distinction between acute and late effects [1]. The term "consequential" has been introduced to define late effects in patients whose acute effects were significant enough that full recovery did not occur. Such late effects are considered to represent a continuum, or consequence, of the initial radiation insult, in contrast to "generic" late effects in patients whose acute toxicity was modest and short-lasting.

Late effects are generally referable to progressive microvascular obliteration [2] and an increasingly dense fibrosis, [3] with osteoradionecrosis (ORN) one of the more feared and destructive [4-7]. ORN is defined as localized ulceration or necrosis of mucosa, with exposed devitalized bone, commonly involving an extraction site that has failed to heal for at least three months. ORN is associated with pain and considerable morbidity, occurring in the absence of bisphosphonates, and persisting or recurrent malignancy [7-11]. ORN is frequently progressive, resulting in greater degrees of exposed bone, loss of alveolar bone height and density, pathologic fracture, intra- and extra-oral fistulas, local and systemic infections [8-10]. Its risk is lifelong and does not diminish with time [12].

First described almost a century ago, ORN became increasingly common beginning in the 1950s, when radiation of oral malignancies evolved to become established practice [2]. While it occurs spontaneously [10], it is frequently a consequence of trauma, with dental extractions a leading cause [10, 14-17]. The mandible is the dominant site. A lower incidence in the maxilla is considered due to its better vascularity, less corticated

bone, [12, 15] and because it frequently lies beyond the RT portal.

Given the risk posed by post-RT dental extractions, some medical practitioners have elected to render patients completely edentulous in the weeks prior to RT, regardless of their state of dental health [14, 18]. This aggressive approach did not, however, eliminate all trauma-induced causes. Ill-fitting dentures, and dentures that fitted well initially but not replaced over time secondary to bone and soft tissue retraction, were prone to damaging oral mucosa [14, 18]. Removal of all teeth, healthy or otherwise, is not common practice [19]. Current standard of care involves meticulous dental evaluation, with provision of urgent repairs and restoration in the weeks prior to RT [19, 20-21]. Extractions are limited to non-restorable teeth, ideally involving minimal surgical trauma and bone manipulation. Alveoloplasty and suturing of sockets further reduce risk [10]. Even where pre-RT oral health is considered optimized many patients will eventually require extractions in the months and years that follow [19, 22-23].

Having introduced a scientific basis for hyperbaric oxygen (HBO_2) in the treatment of established ORN [2, 4], Marx, et al. sought to determine if HBO_2 could prevent ORN secondary to dental extractions in high-risk patients [24]. Seventy-four patients formed the study population, each with an indication for removal of one or more teeth from a segment of mandible irradiated to greater than 6,000 centigray (cGy). Randomization was to perioperative penicillin or perioperative HBO_2. A total of 135 teeth were extracted from the 37 patients in the penicillin group, 11 (29.9%) of whom had 31 unhealed socket wounds at six months. In the HBO_2 group 156 teeth were extracted from 37 patients, two (5.4%) of whom suffered four unhealed socket wounds at six months. Clinical and radiographic evidence of ORN was more extensive in the 11 penicillin group patients compared to the two HBO_2 group patients.

Largely on the strength of these results and absent independent controlled clinical corroboration, HBO_2 prophylaxis became a practice recommendation [25], with this single study increasingly considered conclusive evidence of efficacy [6, 19, 26-28].

A National Cancer Institute monograph, published in follow-up to a consensus development conference on oral complications of cancer therapies, concluded, in part that:

> *'For patients who are thought to be at particularly high risk of developing ORN, pre-extraction HBO_2 should be considered'* [29].

Several U.S. commercial purchasers of health care subsequently added ORN prophylaxis to their list of HBO_2 reimbursable indications.

A number of earlier publications lent support to the HBO_2 prophylaxis protocol [27-28, 30]. As it was essential standard of care, some considered it unethical to randomize patients not to receive it [27-28]. A later report of 40 patients treated in accordance with the Marx prophylaxis protocol noted that all had achieved full mucosal healing immediately upon completion of postoperative HBO_2 [31]. In 19 patients with six-month follow-up data available, however, three (15.8%) had subsequently been diagnosed with ORN, representing a 7.5% incidence for the entire cohort.

Two invited papers in a journal section dedicated to clinical controversies in oral and maxillofacial surgery offered opposing views regarding the value of HBO_2. Lambert, et al. were of the opinion that:

> *'If teeth are unrestorable and require extraction after radiation, HBO prophylaxis should be considered the treatment of choice'* [6].

They based this recommendation on their retrospective long-term data available for 47 of 75 patients who had undergone prophylactic HBO_2 therapy. The RT dosing ranged from 4,500-7,400 cGy, and was unknown in six patients. None developed ORN at a mean follow-up of 2.9 years. Clayman argued:

> *'Data do not support the mandatory use of HBO_2 before removing teeth in irradiated mandibles, particularly when one considers that in the most recent reports of ORN after dental extractions the rate was only 2.1%'* [32].

Clayman had reviewed ORN incidence following dental extractions from 1968 onward, referencing 32 publications. His basis for a 2.1% incidence was the sum of four more recent reports, one of which involved a single patient.

Several other publications appeared to question the necessity of HBO_2 prophylaxis. Makkonen, et al. reported no instances of ORN following 139 extractions, 45 prior- and 94 post-RT, in 92 patients [33]. Extractions involved anterior, mid-level and posterior teeth from both the maxilla and mandible; median dose appeared to be 6,100 cGy (3,000-6,500 cGy), so some patients would likely be low-risk. One case did occur at an

unrelated site. General dentists undertook the majority of extractions. Maxymiw, et al. examined the incidence of ORN after tooth extraction in 72 patients, involving conservative surgical techniques not otherwise defined [34]. A total of 449 teeth were extracted; interestingly only 196 (44%) were within the RT treatment volume. It could be speculated that differences in ORN incidence are, in part, the relationship between extraction sites and treatment volume. Median prescribed tumor dose was 5,000 cGy (2,500-8,400 cGy), so this cohort also involved some low-risk patients, and median follow-up was 4.8 years. There were no ORN cases. Sulaiman, et al. summarized the Memorial Sloan Kettering Cancer Center experience involving 187 (16%) of 1,194 head and neck cancer patients who had undergone extractions [19]. Follow-up averaged 22 months, with a median of 11 months. Overall ORN incidence was 0.92%. Dosing ranged from 5,000 to >7,000 cGy in 162 (87%) patients.

Lye, et al. reported a 1.9% ORN incidence at just 12 weeks in 40 patients who underwent 155 extractions, also in the absence of perioperative HBO_2 [35]. While total RT dose ranged from 6,000 to 7,600 cGy, to their great credit these authors had calculated localized radiation absorption (LRA) for every extracted tooth, using RT data and simulation films. Mean LRA was 4,664 cGy. This unique tooth-specific dose may well be representative of LRA in general, when total dose is within the range noted in this report, and involving conventional external beam RT. It would be of considerable academic and clinical interest to undertake such calculations for patients irradiated with current standard of care, namely intensity-modulated RT (IMRT).

Three literature reviews have summarized ORN prevention measures and resulting incidence after dental extractions post-RT. Koga, et al. suggested that HBO_2 appeared to have a favorable effect, contributing to a low frequency of complications [36]. Following a systematic review of 696 retrieved citations and reduced to 14 acceptable publications addressing perioperative HBO_2, Fritz, et al. concluded:

'*…there is currently insufficient information to show that the use of HBO_2 reduces the incidence of ORN in irradiated patients requiring tooth extraction*' [37].

Nabil, et al. were of the opinion that based upon weak evidence, prophylactic HBO_2 is effective in reducing the risk of ORN [10]. A recent clinical practice guideline applying GRADE evidence-based methodology (*http://www.gradeworkinggroup.org*) concluded:

'*…certainty of evidence supporting the effect of HBO_2 on the outcome for prevention of mandibular ORN is low*' [38].

Several publications suggest that sentiment has turned against prophylactic HBO_2, and/or better quality research is deemed necessary to determine if it remains justified in the modern era [19, 39-43]. Judged by today's efficacy standards, the 1985 Marx, et al. study had fallen somewhat short [19, 43]. Examples cited included no information on how randomization occurred at the three participating centers, number of extracted teeth per patient (ORN incidence increases with number of concurrent extractions [23]), degree of extraction difficulty/extent of alveolar trauma, and mean time to and from RT. Heyboer, et al. surveyed professional attitudes toward HBO_2 as ORN prophylaxis [39]. A majority of radiation oncology (64%) and hyperbaric physician (82%) respondents recommended its use, although a greater majority (79% and 85%, respectively) believed it important that a new clinical trial was necessary. This latter view was consistent with the most common reason not to refer and employ HBO_2 – namely insufficient evidence of efficacy [39].

Such a trial has since been reported [44]. It took the form of a multi-institutional randomized controlled Phase III study. Primary outcome measure was presence or absence of ORN six months following surgery, the same follow-up period used in the previous trial [24], as determined by a blinded central review of clinical photographs and radiographs. Mean RT dose was 6,300 cGy. A planned interim primary analysis took place when the first 100 patients had reached six-month follow-up. Three ORN cases had occurred in 47 (6.4%) patients randomized to receive perioperative HBO_2, and three cases were also diagnosed in 53 (5.7%) patients randomized as controls (those who did not receive HBO_2). No new cases occurred between six and 12 months in either group. This 6% overall incidence was much lower than anticipated during trial design, yet consistent with recent reports [45-49]. Given the lack of a statistical difference, and in accordance with the Haybittle-Peto stopping rule in effect at the time, further recruitment was deemed futile. The trial's Independent Data Safety and Monitoring Committee recommended closing the trial, which did occur.

Shaw, et al. concluded that adequate power to detect differences in any subsequent ORN prevention trial would be difficult to achieve given its low incidence

[44]. They did suggest as one possible exception a genuinely high-risk subgroup, perhaps made possible through yet-to-be-identified susceptibility biomarkers. Complicating any analysis of preventive measures is that ORN can and does occur in the absence of extractions and other trauma [7, 10-12, 14, 23].

ORN incidence has declined markedly from historical highs that in some reports exceeded 50% [9]. This decline is attributed to comprehensive pre-RT dentition assessment and management protocols that serve to reduce post-RT extraction frequency [11, 21, 50] and more advanced, better-targeted RT [5, 20]. It is unclear if IMRT has further contributed to a reduction beyond that afforded by 3-D conformal RT, since IMRT emerged as standard of care for head and neck cancers in the early 2000s. One systematic review determined weighted evidence for ORN as 7.4% with conventional RT vs. 5.1% with IMRT [5]. Several other reports suggest IMRT may minimize risk [20, 49, 51-52]. Caparrotti, et al. examined ORN incidence following IMRT treatment of oropharyngeal cancer in 1,196 patients [53]. Crude overall incidence was 6%, with actuarial rates of 3%, 5% and 7% at years one, three and five, respectively. A study specifically comparing IMRT impact on ORN incidence found no improvement over non-IMRT [54].

Treatment of early/localized mandibular osteoradionecrosis

Localized "minor" ORN is commonly limited to superficial mucosal ulceration with minimal (no more than 2.0-2.5 cm) exposed devitalized bone, present for at least three months and in the absence of infection [7, 9, 15]. Marx challenged the classic understanding of ORN as an osteomyelitic condition within radiation-damaged bone [2, 55]. Analysis of mandible specimens obtained from 26 patients ruled out primary infection. Microorganisms present on the surface of osteoradionecrotic bone were considered to play only a contaminant role. Further analysis led Marx to introduce a new concept of ORN pathophysiology, one involving a sequence of RT-induced hypoxia-hypovascular-hypocellular tissue, which he referred to as the 3-H syndrome, with resulting breakdown and a non-healing wound. In a companion paper, Marx proposed both a new ORN staging system and an algorithmic management approach [4]. Initially described as the Wilford Hall HBO_2 ORN Protocol, Stage 1 involved provision of HBO_2 as primary therapy. Stage 2 represented an indication for surgery, commonly debridement, due to incomplete response to HBO_2 alone. Stage 3 incorporated HBO_2 as perioperative support for surgical management of more advanced disease. Better known today as the Marx Protocol, and in contrast to the previously referenced Marx prophylactic protocol, it became widely adopted as essential standard of care.

An alternative treatment strategy began to emerge several years later. University of Iowa researchers studied pentoxifylline as treatment for soft-tissue radiation injury [56]. They sought to determine if its ability to increase deformability of red blood cells, inhibit platelet aggregation and stimulate prostacyclin would serve to improve perfusion within radiation-damaged microvasculature. Laboratory studies demonstrated diminished lesion severity, prompting their treatment of four radiation-injured patients [57]. Each responded favorably, lending support of the concept of late radiation damage as at least partly a vascular injury. Delanian, et al. proposed an alternative theory to the 3-H syndrome [58], one based upon a complex series of local tissue responses to ionizing radiation. Subsequent generation of reactive oxygen induces an inflammatory response, leading to fibroblast recruitment and accumulation, with extracellular matrix deposition. This process commonly progresses over ensuing months and years, affecting almost every part of the body exposed to radiation. It persists long after the initial insult is no longer present, with dense fibro-inelastic tissue as its endpoint [59].

Tocopherol, a reactive oxygen species scavenger, was added to pentoxifylline (referred to as PENTO) to treat 43 patients presenting with 50 symptomatic areas of soft-tissue radiation-induced fibrosis (RIF) [60]. Uniform clinical regression and functional improvement had occurred at 12 months. While pentoxifylline and tocopherol appear to act synergistically as antifibrotic agents, neither drug given alone appears effective [61]. To determine optimal dosing periods Delanian, et al. treated another 37 superficial RIF patients [62]. Mean maximum effect was 68%, with two-thirds maximum response observed at a mean of two years. They cautioned that risk of rebound exists if the treatment period is too short. That RIF was at least partly reversible represented a highly significant finding, as the long-standing theory was that it was a permanent and irreversible condition [63].

Delanian, et al. subsequently reported a single case of sternal ORN treated with PENTO, but clodronate, a first-generation bisphosphonate, added empirically

because of its ability to inhibit osteoclastic bone destruction [64]. Restoration of the significant bony defect, closure of a fistula and total regression of clinical fibrosis followed a three-year treatment course. Encouraged by these reports, Gothard, et al. studied PENTO in patients with radiation-associated arm lymphedema via a Phase II study, failing to demonstrate benefit [65].

Delanian, et al. continued to employ this multidrug regimen, now referred to as PENTOCLO when clodronate was included, for bony lesions [66-68]. Hayashi, et al. reported 13 cases of mandibular ORN treated with PENTO (i.e., minus clodronate) in identical dosage to that used by the Delanian group [69]. Eleven patients resolved, one did not, and the other remained under care. Treatment time averaged 13.5 months. Another publication described three mandibular ORN patients who healed with PENTO therapy, including one significant fracture [70]. Patel, et al. reported resolution of ORN (85% mandible, 15% maxilla) in 14 (56%) of 25 patients treated with PENTO [71] McLeod, et al. were unable to duplicate these healing responses in 12 cases of mandibular ORN [72].

Common PENTOCLO dosing involves twice-daily 400-mg pentoxifylline (800 mg/day), twice-daily 500-IU vitamin E (1,000 IU/day), and 1,600-mg clodronate once daily Monday-Friday [67]. Less well defined is treatment duration, which is invariably extensive. It frequently extends beyond six months [60, 66]; in some cases two to three years may be necessary [58].

Several recent reviews make favorable reference to PENTOCLO as treatment for early-stage ORN. McCaul considered it a potentially exciting pharmacologic frontier but emphasized the need for high-quality clinical trial evaluation [73]. McCaul believes acceptance has been generally slow, in part because of traditional thinking of ORN as a surgical disease, and adds that some who deal with an increasing burden of bisphosphonate-induced jaw necrosis may find it difficult to introduce clodronate. Lyons and Brennan reviewed the ORN literature related to PENTO and PENTOCLO [74]. They considered prevailing evidence promising, despite the absence of high-quality trials, likewise arguing their urgent need. Rivero, et al. add to the growing assessment that on the strength of limited studies, and despite that many have come from a single research group, this oral antioxidant approach appears promising treatment for ORN and late radiation-induced injury at other anatomic sites [75]. Strojan, et al., writing on behalf of the International Head and Neck Scientific Group (*www.ihnsg.com*), summarized head and neck cancer treatment late sequelae after RT [76]. Conclusions regarding HBO_2 were generally favorable, as they were for PENTOCLO, but high-level evidence was again noted to be in short supply for both interventions. A 2016 analysis of conservative management of mandibular ORN, with similar encouraging perspectives to those referenced above, added that a multi-institutional Phase II ORN trial is currently under way, comparing HBO_2 therapy with or without PENTOCLO [77]. An equivalence or superiority trial directly comparing HBO_2 to PENTOCLO would also seem worthwhile.

PENTO use has extended to ORN prophylaxis [78].

As late consequences of RT, microvascular impairment and fibrosis appear to coexist [2]. As the principal promoters of the fibroatrophic theory, however, Delanian, et al. appear to discount the significance of progressive obliterative endarteritis, as they do HBO_2's ability to overcome it. Whether one pathophysiologic state induces the other, or that they represent entirely independent processes is not entirely clear. A 2003 review of radiation effects on normal (non-malignant) tissue did suggest, at least, that fibrosis reflects (and is therefore a consequence of) microvasculature damage [79]. Hopewell, et al. observed that radiation-induced endothelial cell occlusion of the blood vessel lumen preceded fibrosis by several months [80].

A 2018 survey of oncology and reconstructive surgery specialists within the British Association of Oral and Maxillofacial Surgeons sought to determine the extent of oral antioxidant treatment of ORN. Use of PENTO, and to a lesser degree PENTOCLO, was widespread among 101 respondents representing 33 UK units [81]. This practice was in conflict with National Institute for Health Care Excellence (NICE) guidelines that state PENTO/PENTCLO should be used only when part of a clinical trial [82]. This document carries the same clinical use guideline for HBO_2 therapy [82], suggesting to NICE a paucity of efficacy data for both therapies. While many appear to await better data, PENTOCLO is clearly gaining acceptance as a treatment option for early-stage ORN [81, 83-84]. Its use is associated with much longer treatment periods than a typical course of HBO_2 therapy, but its ready availability, low cost, low risk, and avoidance of daily travel to and from a hyperbaric facility appear attractive offsets to some. Certainly on the strength of published literature, for HBO_2 to remain clinically relevant, better-quality efficacy evidence is essential.

Treatment of advanced mandibular osteoradionecrosis

The long-established Marx staging system [4], one based in part on response to HBO_2, has given way to staging schemes more in keeping with how surgeons diagnose and manage mandibular ORN [15, 85-86]. Several other schemes exist, although there is presently no consensus regarding which is most appropriate. Marx Stage 3 addressed advanced disease [4]. Following a course of preoperative HBO_2, patients would undergo a transcutaneous continuity resection of the involved portion of the mandible and excision of any necrotic soft tissue. At the time of the protocol's development, observation of bleeding bone represented the best determinant for resection margins, although some would include tetracycline fluorescence labeling. Application of an external fixation device maintained temporary mandible alignment in this era of two-stage reconstruction. In time, fixation evolved to internal devices. Another course of HBO_2 followed postoperatively to support surgical wounding of tissues still considered at risk. After an interval of two to three months, definitive bony reconstruction, typically involving a titanium plate and a cancellous bone filled metallic carrier or cadaveric crib, represented completion of the protocol.

Time to effect Stage 3 was in the order of 20 weeks, somewhat longer in those who had progressed from Stage 1. Many patients would have considered this a small price to pay for effective repair of a condition historically associated with high failure rates, and few would argue that the Marx protocol was not a management step change of some magnitude. There were drawbacks, however. HBO_2 was not widely available at the time and considered costly. Marx was able to show that as a line item cost it was indeed high, but a patient's total health care cost was actually lower than without perioperative HBO_2, such was its additive effect on disease resolution [87]. Further, the time-intensive requirement for completion of HBO_2 was difficult for some surgeons to reconcile, their preference being to operate with minimal delay.

Shortly after introduction of the Marx protocol another significant step change occurred, this one in the form of a single-stage mandibular repair involving free fibular bone [88]. This technique has been refined to the point that radical resection and microanastomosed myocutaneous free fibular flap reconstruction are increasingly considered to represent standard of care [8, 15, 22, 89]. While several other bone donor sites are used, the fibular offers many advantages [90]. This flap type not only allows direct reconstruction of the bony deficit, it provides healthy soft tissue and a skin paddle to facilitate tension-free closure of heavily irradiated, fibrotic inelastic skin that would otherwise be difficult to close primarily [8].

In the reconstruction of advanced cases, some suggest that preoperative HBO_2 only serves to delay definitive therapy [20, 23] One institution specifically reported its abandonment of HBO_2 upon introduction of vascularized free fibular flap procedures, as it no longer offered significant benefit and its high costs were no longer justified [15].

These intricate and challenging reconstructions are generally successful in those who have appropriate training, caseload and mastery, but are not without acute and late complications [91-94]. A commonly reported use of osteomyocutaneous free fibular grafts is primary reconstruction following resection of oral malignancies, and complications are common with or without preoperative RT [95-97]. While complication rates may approach and even exceed 50%, eventual overall clinical resolution is often high [91, 97-98]. No significant differences were evident in a comparison of complications in free flap (76% fibula) reconstruction for ORN in patients with or without HBO_2 therapy [93], with a marginally significant increase infection rate noted in the HBO_2 group. Gal, et al. reported a significantly higher post-mandibular free flap reconstruction complication rate (52% vs. 22%) in Marx Stage 3 patients who had advanced from lesser stages following HBO_2 therapy and surgical debridement compared to those who presented primarily with Stage 3 and had not received HBO_2 [91]. Overall complication rate was 43%, yet 29/30 patients achieved ORN resolution. Infection rates were also significantly higher in the HBO_2-treated patients. This group did emphasize that because only 3/30 patients had received perioperative HBO_2, no comparison could be made about its potential value.

As noted, reconstruction of the radiation-damaged mandible increasingly involves free fibula flaps in the absence of perioperative HBO_2. When HBO_2 is mentioned [99] the Annane, et al. clinical trial is commonly cited as evidence that it offers no benefit [100]. Not as commonly cited is reference to the trial's critical flaws [101-103]. It is unfortunate that no formally published efficacy data is able to substantiate HBO_2 in the modern reconstruction era. An open-label

randomized study designed to investigate efficacy and cost-effectiveness of HBO_2 was recently terminated after a decade of recruitment problems, principally patients refusing to participate [104].

In the absence of such data, one might argue the potential for HBO_2 to address postoperative complications not resolved by surgical re-exploration, such as skin paddle ischemia, threatened muscle flap viability, dehiscence and ischemia-reperfusion (I-R) injury. Numerous data suggest HBO_2 improves free flap and microvascular flap survival secondary to primary ischemia, antagonizes I-R injury and enhances wound healing [105]. ORN recurrence may also be amenable to HBO_2, in the manner one might elect to treat its early stages. Convincing surgical colleagues may be a challenge, but these are complex reconstructions, and even partial flap loss is something one absolutely wants to avoid. This possible and limited postoperative role is, however, in contrast to its earlier routine application during mandibular resection and reconstruction.

In concert with these surgical advances have been efforts to better identify resection margins. They include high-resolution computed tomography [106] real-time optical microvascular *in-vivo* imaging [107], three-dimensional isodose curve visualization, [108] and Eppendorf probe-assessed bone oxygen partial pressure [109]. Tetracycline bone fluorescence labeling continues to appear helpful [110]. Resection with a 1-cm margin beyond imaging guidance or until appearance of bleeding healthy bone remains a common standard [8]. Margin perfection remains something of a challenge. Histological confirmation of fully resected necrotic bone margins does not always tally with progression of ORN [111].

Microvascular-based reconstruction using well-vascularized hard and soft tissue commonly occurs immediately upon resection. The Marx Stage 3 perioperative two-stage protocol was an important development at the time, but the current surgical approach is considered to represent a paradigm shift [20].

Hyperbaric radiation sensitization

More promising is renewed interest in HBO_2 as a radiation sensitizer. Radio resistance secondary to solid tumor hypoxia has challenged radiation oncologists for more than a century [112], with an effective hypoxic sensitizer their apparent "Holy Grail." That search appeared over in 1953 when Gray, et al. reported a threefold increase in the radiobiological effect when tumor-bearing mice were irradiated while breathing 100% oxygen within a hyperbaric chamber [113]. This now highly regarded pioneering observation initially faced considerable opposition [114]. Prominent physiologists were of the opinion that oxygen inhalation would produce a negligible effect on tissue oxygen levels, as hemoglobin was already almost completely saturated. A famous biochemist argued that tumor cells rendered hypoxic would instantly die, and a leading radiopathologist insisted that tumor recurrence arose only from well-oxygenated cells [114].

Undeterred by these criticisms, all eventually proven incorrect, Churchill-Davidson, et al. adapted a one-man recompression chamber within which eight oxygen-breathing patients were irradiated. These investigators sought to determine if observed heightened radiosensitivity was demonstrable histologically [115]. Results were particularly encouraging, prompting additional studies, and by the early 1960s hyperbaric sensitization was gaining popular acceptance. Within a decade, however, it had all but ceased to exist. Anticipated survival rates had not occurred across all tumor types, alternative sensitizers were under study, advanced RT delivery systems made it eventually impossible to irradiate patients while in the chamber, and an apparent increased rate of new primary tumors and distant metastases in hyperbaric irradiated patients was worrisome.

A 1996 report reanalyzed all 32 U.K. National Research Council-sponsored solid tumor trials, involving 8,000 patients over a 30-year period, using modern statistical methodology [116]. Highly significant survival advantages were evident for squamous cell carcinomas (SCC) of the head and neck irradiated in hyperbaric chambers. This encouraging data promoted renewed interest in HBO_2. Japanese researchers had been searching for adjuncts to standard care given consistently poor malignant glioma survival. HBO_2 became that adjunct in several studies [117-121]. As it was no longer technically possible to irradiate patients while in the chamber, they did so immediately upon exit. The basis for this sequential approach was the work of Wells, et al. [122]. Although sample sizes were small, tumor regression and median survival were statistically improved in the HBO_2 group. Several studies have demonstrated the ability of hyperbaric exposure to increase intratumoral oxygen tensions to radioresponsive levels [123-125], other research has identified the ideal maximum interval between exiting the chamber and radiation "beam on" [118, 126].

Three-year glioblastoma survival increased from 4.4% to 10.7% in one comparative analysis of 500 patients studied over a 10-year period at a single institution [127]. These authors attribute this improvement to evidence-based surgical and oncology strategies practiced in multidisciplinary setting. One might assume therefore that this survival level is the best currently achievable. While an encouraging relative change, in absolute terms nine out of 10 patients are not alive at three years. Given preliminary evidence of improved outcomes in the HBO_2 glioma studies, there appears a strong rationale to continue to research its sensitization potential in this highly aggressive cancer.

A Phase I dose escalation trial of locally advanced oropharyngeal SCC resulted in no increased acute toxicities when HBO_2 was combined with chemo-radiation [128]. It proved safe and tolerable when given immediately prior to each radiation treatment. A five-year follow-up on these same patients allowed greater analysis [129]. No long-term toxicities were identified, and while not an outcomes study per se, rates of local recurrence and distant metastases were lower and overall survival higher than reports involving chemo-radiation standard of care at the time this trial was initiated.

To further research this tumor type a multi-institutional Phase II randomized sham-controlled trial is in development (*www.clinicaltrials.gov* NCT03843671; *www.isrctn.com* ISRCTN93840508). It will investigate HBO_2 as a radiation sensitizer of locally advanced SCC of the head and neck.

Several reasons dictated selection of this tumor type, grade and location. The previously referenced U.K. National Research Council data demonstrated a statistically significant survival advantage [116]. Current five-year overall survival rates for Stage 3 and Stage 4 head and neck cancers are approximately 55% to 40% respectively (National Cancer Database *www.facs.org*), so is a helpful metric to measure any HBO_2 contribution to this relatively survivable cancer. It is a more common tumor, so any survival enhancement will correspondingly benefit a larger population. It has a relatively high hypoxic fraction, thereby representing a strong biologic plausibility. Finally, a Cochrane Database of Systematic Reviews concluded that there is some evidence that HBO_2 improves local tumor control and lessens mortality in head and neck cancers, yet more research is needed [130].

SUMMARY

Current weight of evidence does not appear to support prophylactic HBO_2 for dental extractions in patients treated for head and neck cancers in this era of exacting pre-RT dental assessment and management, and conformal RT. This position would not apply to patients who did not receive conformal RT. Treatment options for early/localized ORN appear to be a choice between HBO_2 and PENTOCLO. Routinely employed for almost four decades, HBO_2's mechanistic basis is one of induction of angiogenesis within tissues rendered hypocellular-hypovascular-hypoxic, a therapeutic effect recently reaffirmed [131]. Supportive evidence centers on prospective and mainly retrospective clinical reports and case series but no controlled clinical evidence of efficacy. Treatment of radiation-induced fibroatrophic injury with oral antioxidants is the basis for PENTOCLO, first reported for ORN in 2002. Supportive evidence likewise centers on a mix of prospective and retrospective reports, with efficacy data also lacking. HBO_2 therapy has certainly accumulated greater case experience, and on a wider geographic scale. Its treatment course is markedly shorter that PENTOCLO, which may extend for several years, but is limited by its availability and is considerably more expensive.

The decision to choose between HBO_2 and PENTOCLO will essentially come down to one of physician and patient preferences. There are presently no data to suggest superiority of either option, nor any additive or synergistic effects by combining their use. Both therapies would benefit from better-quality supportive data. In the meantime, those who refer to, prescribe or otherwise advocate HBO_2 and remain satisfied with clinical outcomes are unlikely to see any compelling reason to switch to PENTOCLO. The same may hold true for those currently prescribing PENTOCLO, particularly in settings where HBO_2 is not locally available and beyond the means of those responsible for its payment.

Standard of care for ORN necessitating resection and reconstruction increasingly centers on a single-stage microsurgery-based myocutaneous free fibula flap, with perioperative HBO_2 not featuring in recent literature. Acute and late complications with free fibular flaps are common. Those not readily corrected by medical management and/or surgical re-exploration, and any relapsing ORN, may benefit from a course of HBO_2.

For perioperative HBO_2 to remain relevant in the modern surgical era, it must demonstrate improved short- and long-term outcomes through appropriate study and formal reporting.

The potential exists for HBO_2 radiation sensitization to improve local control and overall survival of head and neck SCC. A Phase I trial demonstrated it to be technically feasible, tolerable and safe. A recently developed Phase II trial will investigate efficacy in a multi-institutional setting. Given the consistently high mortality associated with malignant gliomas, an argument exists to investigate adjuncts to chemo-radiation standard care. HBO_2's biological plausibility and preliminary findings suggest it is one such intervention worthy of additional study.

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Conflict of interest statement
The author has declared that no conflict of interest exists with this submission.

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