Hyperbaric oxygen therapy and delayed radiation injuries (soft tissue and bony necrosis): 2012 update

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ABSTRACT / RATIONALE

Informal surveys at CME meetings have shown that approximately one-third of patients in the United States receive hyperbaric oxygen (HBO_2) for delayed radiation injury. More than 600,000 patients receive radiation for malignancy in our country annually, and about one-half will be long-term survivors. Serious radiation complications occur in 5-10% of survivors. A large population of patients is therefore at risk for radiation injury. HBO_2 has been applied to treat patients with radiation injury since the mid-1970s. Published results are consistently positive, but the level of evidence for individual publications is usually not high level, consisting mostly of case series and case reports. Only a rare randomized controlled trial has been accomplished. Radiation injury is one of the UHMS "approved" indications, and third-party payors will usually reimburse for this application. This updated review summarizes the publications available reporting results in treating radiation-injured patients. Mechanisms of HBO_2 in radiation injury are discussed briefly. Outcome is reported on a mostly anatomic basis though due to the nature of the injury a positive outcome at one anatomic site is supportive of HBO_2 at other sites. The potential benefit of prophylactic HBO_2 before frank damage is also discussed in high-risk patients. The concerns of HBO_2 enhancing growth of or precipitating recurrence of malignancy is discussed and largely refuted.

INTRODUCTION

Hyperbaric oxygen (HBO_2) has had one of its most studied and most frequent applications in the treatment of delayed radiation injuries. Informal surveys accomplished by the author at continuing education meetings indicate that roughly one-third of patients treated in the United States receive hyperbaric oxygen for radiation injuries. This application of hyperbaric oxygen to the treatment and prevention of delayed radiation injury will be the topic of this paper. The management of delayed radiation injury, especially when bone necrosis is present, requires multidisciplinary management. The nature of delayed radiation injury, the mechanisms whereby hyperbaric oxygen is effective, clinical results, the effects of hyperbaric oxygen on cancer growth and future areas for research will be discussed.

THE NATURE OF RADIATION INJURY

Radiation injuries should be further subclassified as acute, subacute or delayed complications [1]. Acute injuries are due to direct and essentially immediate cellular toxicity caused by free radical-mediated damage to DNA. Many cells suffer a mitotic or reproductive death, *i.e.*, enough damage has been rendered to the DNA that successful subsequent mitosis is prevented. Acute injuries to normal tissues are usually self-limited within a few weeks and are treated symptomatically. However, they can be very debilitating during their duration. Subacute injuries are typically identifiable in only a few organ systems. Subacute injuries have been shown to occur in the lung with a clinical syndrome mimicking bronchitis (radiation pneumonitis). They have also been shown to occur in the spinal cord as the result of temporary demyelinization which causes the so-called Lhermitte's syndrome, where patients experience electriclike shocks down their legs with spinal extension. These, too, are generally self-limited but occasionally evolve to become delayed injuries.

Some subacute injuries may persist for several months. No specific treatment is especially effective, although steroids are commonly employed. Delayed radiation complications are typically seen after a latent period of six months or more and may occasionally develop many years after the radiation exposure. Sometimes, acute

injuries are so severe that they never resolve and evolve to become chronic injuries indistinguishable from other delayed radiation injuries [2]. These are termed "consequential effects" and are not characterized by a symptom-free latent period. Often, delayed injuries are precipitated by an additional tissue insult such as surgery within the radiation field.

A role for hyperbaric oxygen in acute and subacute radiation injuries has not been well-studied or established, although there is some interest in pursuing this application [3].

THE ETIOLOGY OF DELAYED RADIATION INJURY

The exact causes and biochemical processes leading to delayed radiation injury are complex and only partially understood at this time. In virtually all organ systems that demonstrate radiation damage, we observe vascular changes characterized by obliterative endarteritis. Because hyperbaric oxygen has been shown to enhance angiogenesis in hypoxic tissues, the hyperbaric oxygen community has postulated that the enhancement of angiogenesis was the primary, if not the sole, therapeutic effect of hyperbaric oxygen in radiated tissues. Some radiation biologists are now convinced that in some organ systems vascular changes play a relatively minor role in the evolution of delayed radiation injury [4].

A more complex model of radiation damage continues to evolve in the radiation oncology community. In the past, radiation oncologists had made a distinction between the causes of acute and delayed injuries. The belief was that they were not directly related. Indeed, it is not uncommon to find a patient with serious acute reactions who will not suffer significant delayed complications or someone with severe delayed complications who had experienced no worse than minor acute reactions to the radiation. Radiation researchers now appreciate that the process of radiation injury begins at the time of radiation treatment and involves the elaboration and release of many bioactive substances including, very prominently, fibrogenetic cytokines [5].

A major mechanism whereby therapeutic radiation inflicts damage on normal tissues has been termed the fibro-atrophic effect [4]. This model emphasizes the consequences of the observed depletion of parenchymal and stem cells and de-emphasizes the impact of vascular damage. It also highlights the exuberant fibrosis usually found in severely damaged irradiated tissues [4-8]. In this model vascular damage and stenosis continue to be recognized as a consistent finding in tissues exhibiting radiation damage including frank necrosis; however, endarteritis as a causative factor for delayed radiation injuries is de-emphasized.

A recent review of the delayed fibro-atrophic effects of radiation has been accomplished by Fleckenstein *et al.* [5]. This paper identifies TGF-beta as the most frequently studied cytokine associated with radiation injury. Additional cytokines associated with radiation injury include IL-1, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, TNF-alpha and GMCSF.

Many studies of cytokines and radiation injuries have been accomplished in animal models of radiation-induced pneumonitis [9]. At the present time, we are not able to make practical clinical application of these observed associations. No single marker is likely to provide us with a reliable estimate of future radiation damage [10]. Similarly, no practical strategies have as yet been developed to prevent or reduce the production of these cytokines or reduce their impact in a prophylactic fashion. We know that there is a very wide range of tolerance to radiation by individual patients and that some patients are much more sensitive to radiation injury. If reliable predictors of delayed radiation injury were available during or before treatment, adjustments to the radiation dosing scheme could be made for the radiosensitive patient. Some patients might be advised to seek alternative therapies instead of radiation. Moreover, prophylactic interventions such as hyperbaric oxygen or other yet-to-be-developed pharmacologic interventions could possibly be applied during the latent period but before the manifestation of the chronic injury. The hope and expectation would be that, by identifying a group at risk and intervening in this group before manifestation of the injury, delayed radiation injury could be prevented or at least reduced in its severity. Obviously, this postulate will have to be subjected to clinical trials, and the most important consideration is to do nothing that jeopardizes tumor control.

THE EFFECTS OF HYPERBARIC OXYGEN ON IRRADIATED TISSUES

Because a consistent cause and manifestation of radiation injury is vascular obliteration and stromal fibrosis, the known impact of hyperbaric oxygen in stimulating angiogenesis is an obvious and important mechanism whereby hyperbaric oxygen is effective in radiation injury. HBO_2 induces neovascularization in hypoxic tissues. Marx [11] has demonstrated the enhanced

vascularity and cellularity in heavily irradiated tissues after hyperbaric oxygen therapy by comparing histologic specimens from patients pre- and post-hyperbaric oxygen. Marx [6] has also demonstrated the serial improvement in transcutaneous oxygen measurements of patients receiving hyperbaric oxygen as an indirect measure of increased vascular density. Marx *et al.* [12] in an animal model have shown increased vascularity in rabbit mandibles after exposure to hyperbaric oxygen.

Feldmeier and his colleagues [7,8] in a murine model of radiation damage to the small bowel have shown that hyperbaric oxygen given seven weeks after radiation can reduce the degree and mechanical effects of fibrosis by being applied prior to the manifestation of radiation injury. Assays of the murine bowel for collagen content included a mechanical stretch assay of compliance as well as quantitative histologic morphometric assays of fibrosis in the tunica media of the animal bowel utilizing Mason's trichrome staining.

This author has personally observed significant reduction in the woody fibrosis of soft tissues seen frequently in head and neck cancer patients after radiation with a course of hyperbaric oxygen intended to treat mandibular necrosis. To my knowledge, this effect has not yet been systematically studied.

The hyperbaric study group headed up by Dr. Thom [13,14] at the University of Pennsylvania has published studies demonstrating the mobilization of stem cells mediated through nitric oxide with HBO_2. These papers include a group of head and neck cancer patients who had received radiation treatments. A putative effect on increasing stem cells at the site of radiation injury is confirmed to some extent by Marx's [6] demonstration of increased cellular density in histologic preparations from patients who have received hyperbaric oxygen for mandibular osteoradionecrosis.

The impact of hyperbaric oxygen in terms of its beneficial effects is likely to involve all three of the above mechanisms in irradiated tissues:

1) Hyperbaric oxygen stimulates angiogenesis and secondarily improves tissue oxygenation;
2) Hyperbaric oxygen reduces fibrosis; and
3) Hyperbaric oxygen mobilizes and induces an increase of stem cells within irradiated tissues.

Hyperbaric oxygen has been applied as a therapy for delayed radiation injury for more than 30 years. Hyperbaric oxygen also has a frequent application in the prevention of mandibular osteoradionecrosis when dental extractions are required from heavily irradiated mandibles. The following sections will address the application of hyperbaric oxygen to radiation complications on an anatomic basis beginning with mandibular osteoradionecrosis.

HYPERBARIC OXYGEN AS TREATMENT FOR MANDIBULAR RADIATION NECROSIS (ORN)

The most widely applied and most extensively documented indication for hyperbaric oxygen in chronic radiation injury is its application in the treatment and prevention of radiation necrosis of the mandible. Multiple publications describing the use of hyperbaric oxygen in the treatment of mandibular necrosis have appeared in the medical literature since the 1970s.

The likelihood of mandibular necrosis as a result of therapeutic radiation varies widely among several reports. Bedwinek [15] has reported a 0% incidence below doses of 6,000 cGy increasing to 1.8% at doses from 6,000 to 7,000 cGy and to 9% at doses greater than 7,000 cGy. In his comprehensive review of radiation tolerance, Emami [16] estimates a 5% incidence when a small portion of the mandible (less than one-third) is irradiated to 65 Gy or higher and a 5% incidence at 60 Gy or higher when a larger volume of the mandible is irradiated. The recent application of IMRT (intensity-modulated radiation therapy) has been reported to reduce mandibular radiation necrosis compared to older radiation techniques [17]. It has been reported that 85% or more of cases resulting in exposed mandibular bone will resolve spontaneously with conservative management [18]. Unfortunately, the remaining cases generally become chronic and may become progressive, often further complicated by associated soft tissue necrosis.

Much of the early work in this area considered radiation-induced mandibular necrosis to be a subset of mandibular osteomyelitis [11]. Also, hyperbaric oxygen was delivered along with antibiotics frequently as treatment for mandibular necrosis without appropriate surgical management after failure of more conservative therapy. Although many cases would show temporary improvement, almost all cases of moderate to severe ORN would recur if hyperbaric oxygen was administered without appropriate surgical intervention [19].

Robert Marx D.D.S. [19,20] elucidated many basic principles in the etiology and management of mandibular ORN which have led to a rational approach to its management. He has provided several key principles in the understanding of the pathophysiology of mandibular necrosis. He has demonstrated that infection is not the primary etiology of mandibular necrosis by obtaining

deep cultures of affected bone and showing the absence of bacteria. We now understand that osteoradionecrosis is the result of an avascular, aseptic necrosis. Marx [6] has also shown that for hyperbaric oxygen to be consistently successful, it must be combined with surgery in an optimal fashion. Marx has developed a staging system for classifying mandibular necrosis. This staging system is applied to determine the severity of mandibular necrosis. In addition, it permits a plan of therapeutic intervention, which is a logical outgrowth of the stage/severity of necrosis.

Stage I ORN

This stage includes those patients with exposed bone who have none of the serious manifestations found in Stage III as described below. Generally, before hyperbaric oxygen, these patients have had chronically exposed bone or they have rapidly progressive ORN. These patients begin treatment with 30 HBO_2 sessions followed by minor bony debridement. If these patients' response is adequate, an additional 10 daily treatments are given, and the patients are followed to complete clinical resolution.

Stage II ORN

If patients are not progressing appropriately at 30 daily treatments or if a more major debridement is needed, they are advanced to Stage II and receive a more radical surgical debridement in the operating room followed by 10 postoperative treatments. Surgery for Stage II patients must maintain mandibular continuity. If mandibular segmental resection is required, patients are advanced to Stage III.

Stage III ORN

In addition to those failing treatment in Stage I or II, patients who present initially with grave prognostic signs such as pathologic fracture, orocutaneous fistulae or evidence of lytic involvement extending to the inferior mandibular border are treated as Stage III from the outset. When a patient is assessed to be at Stage III, mandibular segmental resection is a planned part of the treatment. In Stage III, patients are entered into a reconstructive protocol after mandibular resection. Marx has established the principle that all necrotic bone must be surgically eradicated here just as in Stages I and II. Stage III patients receive 30 daily hyperbaric treatments prior to mandibular resection followed by 10 post-resection treatments.

Typically after a period of several weeks, the patients complete a reconstruction, which may involve various surgical techniques including free flaps or myocutaneous flaps. In the original reports, the reconstruction made use of freeze-dried cadaveric bone trays from a split rib or iliac crest combined with autologous corticocancellous bone grafting. In his original work at Wilford Hall USAF Medical Center, Marx had reconstruction patients complete a full additional course of hyperbaric treatments in support of the reconstruction. Marx has subsequently found that the vascular improvements accomplished during the initial 40 hyperbaric exposures are maintained over time, and patients can undergo reconstruction without a second full course of HBO_2. Patients do receive 10 hyperbaric treatments after the reconstructive surgery to support initial tissue metabolic demands.

Marx [6] has reported his results in 268 patients treated according to the above protocol. In his hands with this technique, successful resolution has been achieved in 100% of patients. Unfortunately the majority of patients (68%) required treatment as Stage III patients necessitating mandibular resection and reconstruction. Dr. Marx requires that patients achieve reasonable cosmetic restoration as well as the success in supporting a denture before he counts them a success. These two issues, cosmesis and restoration of dentition for mastication, are necessary components in improving quality of life in this group of patients.

Feldmeier and Hampson [21] published a review of hyperbaric oxygen in the treatment of radiation injury in 2002. A total of 14 papers reporting the results in the treatment of mandibular necrosis were included. All but one of these was a case series. A single study by Tobey *et al.* [22] was a positive randomized controlled trial. It was a small study, with only 12 patients enrolled; however, it was double-blinded and reported to be a positive trial by the authors. Details of randomization and outcome determinants were not clearly stated. Patients received either 100% oxygen at 1.2 atmospheres absolute (atm abs) or 2.0 atm abs. The paper states that those treated at 2.0 atm abs "experienced significant improvement" compared to the control group.

Of the reports included in this review paper of 2002, only one report, the publication by Maier *et al.* [23], failed to report a positive outcome in applying hyperbaric oxygen to the treatment of mandibular ORN. Maier and colleagues added hyperbaric oxygen to their management only after the definitive surgery was done. They failed to heed Marx's guidance that the optimal management of mandibular ORN requires that the majority of HBO_2 be given prior to surgical debridement, resection or reconstruction in order to improve the quality of tissues prior to surgical wounding.

Since the review by Feldmeier and Hampson [21], several papers have been added to the literature. A multi-institutional randomized controlled trial by Annane *et al.* [24] reported negative results in their study applying hyperbaric oxygen to Marx Stage I ORN. These results have created a stir in the hyperbaric oxygen community and prompted criticism of its methods from several sources. Patients were randomized to receive either 90 minutes of 100% O_2 at 2.4 atm abs or a breathing gas mix equivalent to air at sea level for 30 daily treatments. The study design has received criticism from several circles. The most serious flaw in the study design was its failure to adhere to Marx's guidance and to integrate hyperbaric oxygen into a multidisciplinary approach to ORN treatment. The study's apparent intent was to investigate whether the application of hyperbaric oxygen could obviate the need for surgery in early mandibular ORN. It is not surprising that the study had negative results, because more than two decades earlier Marx had shown an absolute necessity of surgically eradicating all necrotic bone. The need to debride all necrotic bone to achieve resolution was also confirmed by Feldmeier *et al.* in their review of chest wall necrosis, including some cases with ORN of the ribs and sternum [25]. Results are very poor overall in the Annane trial compared to other modern trials for what constitutes a Marx Stage I ORN, with only 19% in the hyperbaric group and 32% in the control group achieving resolution [24].

Additional criticisms of this study by Annane [24] been made. Moon *et al.* [26] have shown that nearly two-thirds of the hyperbaric group received fewer than 22 hyperbaric treatments. Laden [27] points out that the patients assigned to the control group had a risk for developing decompression sickness with the gas mix they breathed (9% oxygen and 91% nitrogen) at 2.4 atm abs. This gas mix was designed to provide an inspired oxygen partial pressure equivalent to air at sea level.

In another recent report, Gal and associates [28] have published their results in treating a series of 30 patients with Marx Stage III mandibular ORN with debridement and reconstruction employing microvascular anastomosis. Twenty-one of these patients had previously been treated with hyperbaric oxygen without resolution. The specific number and profile of hyperbaric treatments was not described for any of these patients. At least some patients had some debridement prior to coming to Gal.

Once in Dr. Gal's hands, all patients had appropriate debridement and reconstruction with free flaps. Those patients who had not seen hyperbaric oxygen previously had a complication rate of 22%, while the group who had received at least some hyperbaric oxygen had a much higher rate of complications – 52%. Of course, this was not a randomized trial, and even the authors suggest that the hyperbaric group may have represented a group with more refractory mandibular ORN. Obviously, those principles previously established by Marx, *i.e.*, an emphasis on presurgical hyperbaric oxygen, debridement of all necrotic bone followed by reconstruction with postoperative hyperbaric oxygen were not followed. The authors of this paper also discuss that Marx Stage III ORN patients represent a heterogeneous group with a broad range of injuries, severity of injuries and a subsequent broad range of outcomes.

Teng and Futran [29] have recently published their opinion that hyperbaric oxygen has no role in treating ORN. Their article presents no new clinical data and is a review article. The authors base their conclusions on the Annane study and the advancement of the fibroatrophic model of radiation injury as now dominant in the opinion of many experts of radiation pathology. Mendenhall [30], a radiation oncologist from the University of Florida, in an editorial accompanying the Annane paper in the *Journal of Clinical Oncology*, points out that the Annane paper was underpowered and therefore subject to question. He goes on, however, to state his belief that hyperbaric oxygen is not indicated for mandibular ORN although he remarks that it is hard to understand why the HBO_2 group in the Annane study did worse than the control group.

Hampson *et al.* [31] have recently reported a series of 411 patients treated for radiation injury involving multiple anatomic sites at the Virginia Mason Hyperbaric Center since 2002. The outcome of many of these patients has been previously reported in earlier publications. Among these patients, 62 patients were treated for mandibular necrosis. Forty-three were available for analysis and, among these, 73% showed resolution, 21% had 50-90% improvement, and the other 5% were unchanged.

Suffice it to say that recent papers addressing the efficacy of hyperbaric oxygen in the treatment of ORN have expressed divergent opinions in regard to the efficacy of HBO_2. Only one of these recent publications was a randomized controlled trial, and it is subject to the criticisms in design discussed above. If we look at the total body of literature reporting the impact of hyperbaric oxygen on mandibular ORN, we find the following: In the publications reviewed in the Feldmeier/Hampson review [21], a total of 371 cases of mandibular ORN are reported with a positive outcome in 310, or

83.6%. Unfortunately, some of the papers report improvement rather than resolution as their outcome determinate. Of course a better determination of outcome would be resolution. In Marx's [6] reports, resolution is reported in 100%. Marx also indicates that success in Stage III patients requires not only re-establishment of mandibular continuity but also rehabilitation with a denture for cosmesis and mastication. By contrast, if we look at the recent "negative" trials, only 22 patients are included in the Gal report [28] and 31 patients randomized to hyperbaric oxygen in the Annane [24] trial, for a total of 53 patients. In the recent review by Hampson *et al.* [31], in 43 evaluable patients 73% had complete resolution. Practitioners of hyperbaric oxygen who treat mandibular ORN must do so in a multidisciplinary manner and insure that treatment includes an oral surgeon who can accomplish the needed extirpation of all necrotic bone. For Stage III patients, after resection and resultant discontinuity, patients must have the advantage of skilled reconstructive surgeons and the best modern surgical techniques.

HBO_2 FOR PROPHYLAXIS OF OSTEORADIONECROSIS

Extraction of teeth from heavily irradiated jaws is a common precipitating factor for mandibular necrosis. Marx [32] has published the results of a randomized prospective trial wherein patients who had received a radiation dose of at least 6,800 cGy were randomly assigned to pre-extraction HBO_2 *vs.* penicillin prophylaxis. Those patients assigned to the hyperbaric group completed 20 pre-extraction daily HBO_2 treatments with 10 additional post-extraction daily hyperbaric treatments. Thirty-seven patients were treated in each group. In the penicillin group, a total of 29.9% of patients developed ORN while only 5.4% of patients in the hyperbaric group developed necrosis. Also, the severity of subsequent ORN was more pronounced in the penicillin group, with nearly three-quarters requiring treatment as Stage III patients; neither patient with ORN from the hyperbaric group required a resection and reconstruction, and both resolved with treatment as Stage I ORN patients with additional hyperbaric oxygen and appropriate debridement.

The important principles advocated by Marx in the treatment as well as prevention of ORN include an emphasis on pre-surgical hyperbaric oxygen to improve tolerance to surgical wounding. Other practitioners have applied these principles established by Marx and his colleagues and have had similar success in the prevention and treatment of mandibular necrosis.

Two additional case series reporting positive outcomes in applying hyperbaric oxygen prior to dental extractions were included in the review by Hampson and Feldmeier [21]. In the publication of Vudiniabola *et al.* [33] following the Marx protocol in ORN prophylaxis, one of 29 patients experienced ORN, while in a similar case series from David *et al.* [34] one of 24 patients experienced mandibular ORN after extractions from a radiated mandible following the prophylactic application of hyperbaric oxygen. If the results from Marx's study are combined with these two cited series, four of 90 patients (4.5%) deveoped ORN after treatment with hyperbaric oxygen. Recall that in Marx's control group when radiation doses exceeded 6800 cGy the resultant incidence of ORN was nearly 30% without hyperbaric oxygen.

More recent publications include the report of 40 patients by Chavez and Atkinson [35] in whom hyperbaric oxygen was applied in the manner prescribed by Marx (20 pre-extraction hyperbaric treatments followed by 10 post-extraction). The authors report the uncomplicated healing of tooth sockets was observed in 98.5% of extractions.

Sulaiman *et al.* [36] from Sloan-Kettering report their results in dental extractions in a series of 187 previously irradiated patients. Only three patients in this group received hyperbaric oxygen, and the authors report that most received radiation doses between 6000 and 7000 cGy. Mandibular ORN developed in only four of the 180 (2.2%). The authors attribute this excellent result to their "atraumatic" technique in extracting the teeth. They question the need for hyperbaric oxygen if their surgical techniques are emulated.

Obviously, though it includes a large number of patients, this report is itself only a case series without controls. Marx's patients in his prophylactic study all had doses of 6800cGy or greater while in the Sulaiman report 68% received doses lower than 6900 cGy. A total of 21% received doses less than or equal to 5900 cGy.

Michael Wahl [37], a dentist in private practice, published a review article in 2006 in the most prominent radiation oncology journal. No new data was presented in this paper. In this review he concluded: "There is insufficient evidence to support the use of prophylactic HBO treatments . . . before extractions or other oral surgical procedures in radiation patients."

Some have suggested that mandibular ORN is decreasing in incidence due to modern radiation techniques, including intensity-modulated radiation (IMRT)

[38]. On the other hand, there has been a major shift to primary radiation with chemotherapy sensitization, requiring higher doses of radiation in an attempt to avoid radical surgical resections. In 2003, Reuther and colleagues [39] from the University of Heidelberg reported their experience in a 30-year review of head and neck radiotherapy. They reported an incidence of ORN in this group of 830 patients as 8.2%. In the recent review by Hampson *et al.* [31], a total of 210 patients were treated prior to dental extractions to prevent frank ORN. One hundred sixty-six patients were available for evaluation, and among this group 92% had no evidence of ORN, and 8% of this group had 50-90% healing of the extraction sockets.

LARYNGEAL NECROSIS AND OTHER SOFT TISSUE NECROSES OF THE HEAD AND NECK

Laryngeal necrosis is an uncommon complication of radiation therapy for head and neck cancer. In well designed and appropriately fractionated radiation treatments, its incidence should be less than 1% [40,41]. However, when persistent edema, fetid breath or visible necrosis persist for more than six months after completion of irradiation, the standard recommendation has been to accomplish a laryngectomy because the likelihood of persistent tumor is very high and because effective therapies to reverse necrosis were not known [42]. Biopsy in order to eliminate the presence of cancer may be necessary. Biopsies, however, must be done with caution and are subject to sampling error. Often, the residual cancer is not readily visible on endoscopy and may be submucosal, thus requiring several random biopsies. Extensive surgical wounding of already injured tissues may further exacerbate tissue damage.

Chandler [43] has established a system to grade the severity of laryngeal necrosis: Most with Grade 1 and 2 levels of necrosis will resolve; patients suffering from Grade 3 or 4 necrosis have a high likelihood of requiring laryngectomy. Five institutions have now published case series in applying hyperbaric oxygen to the treatment of radiation laryngeal necrosis [44-47]. Additionally, a new single case report has also been published [48]. In these five reports most patients were treated for severe laryngeal necrosis (Chandler Grade 3 or 4). The outcome in a total of 43 cases is reported, and only six patients were failures to treatment and required laryngectomy. The other 37 patients maintained their voice box and most ultimately had good voice quality.

In the recent very large case series reported by Hampson *et al.* [31], there were 27 patients treated and evaluable for soft tissue radiation necrosis of the larynx. Improvement by at least 50% was seen in 82% of these patients. Patients were retrospectively graded by the Chandler system described above, and the majority were Grade 3 or 4.

In addition to laryngeal necrosis, there are several published reports addressing the results of hyperbaric oxygen treatment in other soft tissue injuries of the head and neck. Many of these deal with soft tissue necrosis of the neck and failing flaps within irradiated fields. In the textbook *Hyperbaric Medicine Practice,* edited by Dr. Eric Kindwall, Marx [6] reported extensive experience in treating soft tissue radiation injuries of the head and neck. In a controlled but non-randomized report of 160 patients, he compared wound infection, dehiscence and delayed healing in the hyperbaric group *vs.* a control group. He found that HBO_2 patients experienced 6% wound infection *vs.* 24% control; 11% dehiscence *vs.* 48% control; and 11% delayed wound healing *vs.* 55% control. All differences are statistically significant when the chi-square test is applied.

These results have also been duplicated by other authors. Davis and his colleagues [49] have reported successful treatment in 15 of 16 patients with soft tissue necrosis of the head and neck, including many with extensive necrotic wounds.

In 1997, Neovius and colleagues [50] reported a series of 15 patients treated with hyperbaric oxygen for wound complications after surgery within an irradiated field. They compared this group to a carefully matched historical control group from the same institution. Twelve of the 15 patients in the hyperbaric group healed completely, with improvement in two and only one without benefit. In the control group only seven of 15 patients healed. Two patients in the control group also developed life-threatening hemorrhage, and one of these did indeed exsanguinate. Any practitioner experienced in the management of head and neck cancer patients has experienced at least one patient in his or her career who has died from exsanguination as the result of a soft tissue necrosis of the neck which progressed to erode into the carotid artery or other major vessel.

In another group of patients, Feldmeier and colleagues [51] have reported the successful prophylactic treatment of patients undergoing radical surgical resection for salvage of head and neck cancer following failure of initial cancer treatment, which included full-course irradiation. Serious surgical complications, including occasional fatalities, have been reported to occur in

more than 60% of patients undergoing radical surgery within a previously irradiated field without the benefit of HBO_2 [52,53]. With a short course of HBO_2 initiated immediately after surgery (median number of treatments 12), 87.5% of patients healed their surgical wounds with no serious complications. In this group, no deaths occurred in the immediate postoperative period.

CHEST WALL NECROSIS

Radiation therapy after lumpectomy has become the preferred treatment for most early breast cancers. After this treatment, fat necrosis of the intact breast has been reported but is a fairly uncommon clinical problem. Hyperbaric oxygen has not been reported as a therapeutic strategy in this condition.

Radiation therapy is frequently used as an adjuvant treatment following mastectomy in more advanced cancers for large tumors or when axillary metastases are present. When a patient is irradiated after mastectomy, the radiation dose to the skin is intentionally high, with the goal of preventing tumor failure in the dermal lymphatics. As a result of this standard radiation technique, most women irradiated after mastectomy are subject to brisk acute radiation reactions. Some patients experience large areas of moist desquamation with superficial ulceration. Frank necrosis of the chest wall is fairly uncommon but is very difficult to manage when it does occur. Traditional treatment for chest wall necrosis has required extensive surgical debridement and, frequently, closure with omental or myocutaneous flaps originating outside the radiation field to insure vascular supply that is unimpaired by radiation vascular injury.

Hart and Mainous [54] in 1976 reported the successful application of hyperbaric oxygen as an adjunct to skin grafting in women treated for necrosis of the chest wall after mastectomy. Feldmeier and colleagues [25] in 1995 reported the outcome in applying hyperbaric oxygen as treatment of both soft tissue and bony necrosis of the chest wall. In this report, all cancer-free patients who suffered only soft tissue necrosis were treated successfully. However, only eight of 15 patients treated resolved when ORN of the sternum or ribs was present. The common characteristic in all of these failed cases was the failure to eliminate surgically all necrotic bone. As discussed above, Marx had previously demonstrated the necessity of total extirpation of necrotic bone for the treatment of mandibular necrosis. This general principle should apply to osteoradionecrosis at any site. Vanderpuye and his colleagues also discuss the need to address necrotic bone in their review of ORN [55].

Writing from the University of Düsseldorf in 1998 Carl and Hartmann [56] reported a single case of a patient who had experienced painful breast edema following lumpectomy and postoperative radiation. After 15 daily hyperbaric treatments of 90 minutes of 100% hyperbaric oxygen at 2.4 atm abs, the patient experienced complete resolution of pain and edema.

In 2001 Carl and his associates [57] reported the outcome of 44 patients who experienced complications following lumpectomy and irradiation for early breast cancers. These patients were found to have pain, edema, fibrosis and telangiectasias as a consequence of their irradiation. Each patient experienced these complications in various combinations and to varying degrees of severity. The severity of symptoms was assessed with a score for each patient based on a modified scale for late effects in normal tissues subjective, objective, management and analytic scores (LENT-SOMA). Each patient was assessed a score from 1 to 4 in the severity of symptoms in the categories of pain, edema, fibrosis/fat necrosis and telangiectasia/erythema. Only patients with at least Grade 3 pain (persistent and intense) or a summed LENT-SOMA score of 8 were studied.

Thirty-two patients agreed to undergo hyperbaric oxygen treatment, while 12 women refused HBO_2 and constituted the control group. Hyperbaric oxygen treatments resulted in a statistically significant reduction in the post-treatment SOMA-LENT scores in women who received treatment compared to those who did not. Fibrosis and telangiectasia were not reduced. Women in the control group continued to demonstrate symptoms at the completion of the trial, with no improvement in pain or edema. Seven women in the hyperbaric group had complete resolution of their symptoms.

RADIATION CYSTITIS

Radiation therapy is commonly applied to tumors of the pelvis, which include rectal cancers, gynecologic malignancies and prostate cancer. Radiation cystitis is not a common complication but can be very difficult to manage when it does occur. In its most serious manifestations, it may even require cystectomy and diversion of the urinary stream. Conservative measures include the installation of formalin or alum as chemical cautery agents into the bladder lumen. Feldmeier and Hampson [21], in the previously cited review article, discuss 17 papers wherein hyperbaric oxygen has been delivered for this

indication. At the time of this review, the paper by Bevers *et al.* [58] was the largest series. It was a prospective but non-randomized and non-controlled trial. All of the other reports were case series. Many, if not most, of the patients reported in these series and subsequent series had already failed other conservative measures. Since this review article, there have been additional reports of hyperbaric oxygen for radiation cystitis. Neheman *et al.* [59] from Israel have published their results in a case series of seven patients. These patients received a mean number of 30 daily hyperbaric oxygen treatments. Patients were treated at 2.0 atm abs for 90 minutes of 100% oxygen exposure. All seven patients had initial resolution of their hematuria. Two recurred and again received hyperbaric oxygen, with an additional 30 and 37 treatments, respectively. Hematuria again resolved. Another patient had resolution of hematuria after 20 hyperbaric oxygen treatments but had progressive tumor (a primitive neuroectodermal tumor) and died as a result of the malignancy.

In a recent publication by Corman *et al.* [60], the authors report a 2003 series from Virginia Mason Medical Center of 57 patients treated for radiation cystitis with HBO_2. Chong *et al.* [61] have updated this series in 2005 with an additional three patients. At the time of publication this paper represented the largest series of patients treated for radiation-induced cystitis. In this report, the average number of treatments was 33 at 2.36 atm abs for 90 minutes of 100% oxygen. In the first paper, 80% of those treated had either complete or partial resolution. For those experiencing clot retention, six had complete resolution and 26 partial resolution. Eight had no change, and two worsened.

In the second publication, the authors report the importance of early intervention. In their analysis, they found that the rate of improvement increases from 80% to 96% when HBO_2 begins within six months of onset of hematuria. Improvement in clot retention was seen in 100% of those who began treatment within six months. Another notable advantage of this trial is that outcomes were reported at least 12 months after completion of HBO_2 treatment. The evaluation at this point is indicative of a durable response and does not include that group which may see early response but then experience recurrence in a relatively short time period.

Hemorrhagic cystitis is often a serious and, occasionally, a life-threatening disorder. Cheng and Foo [62] have reported their results in treating nine patients with refractory radiation-induced hemorrhagic cystitis without hyperbaric oxygen. Six of these patients required bilateral percutaneous nephrostomies, while three patients required ileal loop diversions of their urinary stream. In spite of aggressive surgical intervention, 44% of the patients in this series died as the result of their cystitis. In another review by Sun and Chao [63], the authors report a 3.7% mortality rate in their review of 378 patients experiencing hemorrhagic cystitis. All of these patients had been irradiated for cervical cancer.

In summary, 18 of 19 published series applying hyperbaric oxygen to radiation cystitis are positive reports. When we combine those patients included in the review by Feldmeier and Hampson [21] with the additional patients reported since then, of the 257 patients in published series 196 (76.3%) had either partial or complete response. This success rate is especially noteworthy when compared to those publications cited above, which note a poor outcome and significant mortality rate when HBO_2 is not employed.

In the recent large review by Hampson *et al.* [31], a total of 44 patients treated for radiation cystitis were evaluable. Many of these were reported by this author and his associates previously. The authors report 57% to have had complete resolution and another 32% to have improved by 50-90%.

RADIATION PROCTITIS AND ENTERITIS

A controlled animal study has been reported by Feldmeier and associates [64,65] wherein HBO_2 was shown to be highly successful in preventing radiation-induced enteritis. In this study, experimental animals received HBO_2 in a prophylactic setting seven weeks after radiation exposure. When animals were euthanized seven months after the radiation exposure, both gross and histologic morphometry demonstrated a statistically significant reduction in signs of enteritis in the experimental group compared to the radiation-only control group. Both quantitative histologic morphometry and a mechanical stretch test demonstrated reduction in submucosal fibrosis and an increase in mechanical compliance for hyperbaric-treated animals.

In the review by Feldmeier and Hampson [21], nine clinical papers reporting the results of hyperbaric oxygen in the treatment of enteritis or proctitis were identified. These publications present a total of 114 cases. Forty-one (36%) of these patients were treated with complete resolution while another 68 (60%) had improved symptoms; 4% of patients had no benefit from treatment.

Bredfeldt and Hampson [66] from Virginia Mason Medical Center have reported in abstract form their

experience in applying hyperbaric oxygen to the treatment of 19 patients with chronic radiation injury to the GI tract [80]. Injuries included radiation proctitis (some with ulceration), gastroduodenal bleeding and an esophageal ulcer. Patients were treated with 30 hyperbaric treatments at 2.36 atm abs. Complete resolution was achieved in 47%, with improvement in another 37%, and no improvement in the remaining 16%. A case report by Neurath and colleagues [67] documents the successful resolution of severe malabsorption due to established radiation enteritis in a 53-year-old female following 20 hyperbaric treatments at 3.0 atm abs for 90 minutes.

Since this review, additional publications on this topic have been published. Jones *et al.* [68] have published their experience in treating 10 patients with HBO_2 for radiation-induced proctitis. Three of their patients had Grade 3 toxicity (bleeding necessitating transfusion). The seven remaining patients had Grade 2 toxicity, due to rectal pain and/or diarrhea. Six of the seven had rectal bleeding but had not required transfusion. Nine of these 10 patients completed treatment without complications. Rectal bleeding resolved in four patients while improvement was seen in three others. Two failed to respond. Rectal pain resolved in three of five patients affected. In those suffering chronic diarrhea, one of five resolved and three improved. Of the 10 patients in this series only two failed to experience demonstrable improvement. In this study median follow-up was 25 months again showing durability.

In another series from Girnius *et al.* [69] from Cincinnati, nine patients with hemorrhagic proctitis were treated with hyperbaric oxygen. Five patients had previously required transfusion, and three had been unsuccessfully treated with argon plasma coagulation or electrocautery. The authors report, with median follow-up of 17 months, complete resolution in seven of the nine. The remaining two had improvement but still had some bleeding.

A large published experience in radiation injury to the GI tract is from the Virginia Mason group [70,71]. These results are published in two papers. A total of 65 patients are reported, 37 male and 28 female. All had endoscopic documentation of their injury. The injuries included 54 rectal injuries, with 15 in the more proximal GI tract (four stomach, seven small bowel, six colon and six duodenum). More than 65 injuries are reported because some patients had multiple injuries. These patients had an initial 30 HBO_2 treatments at 2.36 atm abs for 90 minutes of 100% O_2. In those patients demonstrating a partial response at this point, additional treatments were delivered (six to 30 treatments). Complete response rate overall was 43% (28 patients), and partial response 25% (16 patients). The results were somewhat worse for rectal cancer, with a response rate of 65% compared to 73% for proximal lesions.

When we combine all of those cases from the above citations, we find published experience in 199 cases of proctitis, colitis and enteritis treated by HBO_2 (having combined the total Virginia Mason experience). Eighty of these patients (41%) had complete resolution, while 169 (86%) experienced at least partial response. Only 14% failed to respond at all.

In a randomized controlled blinded trial sponsored by the Baromedical Research Foundation, Clarke *et al.* [72] have reported their results in applying hyperbaric oxygen to patients with refractory chronic radiation-induced proctitis. A total of 150 patients were enrolled in the trial, and 120 were evaluable. Patients were assessed utilizing the SOMA-LENT scoring systems, which have become standard in studies of radiation injuries/complications. Patients in the active arm were treated on 100% O_2 at 2.0 atm abs. Sham patients were exposed to very slightly elevated pressures (1.1 atm abs) breathing air. The intent was to give the control patients the sense of pressurization without enhanced oxygenation.

After 30 treatments, reassessment was made by the referring physician, who was blinded and, in select patients who had shown partial response, an additional 10 treatments were accomplished. Control patients were offered the opportunity to cross over to hyperbaric oxygen, and all but three agreed to do so. With an average follow-up of two years (minimum one year), those patients in the active arm showed a statistically increased improvement in their SOMA-LENT scores (5.00 *vs.* 2.61) with a p-value of 0.0019. Responders in the active arm were 88.9% *vs.* 62.5% in the control arm (p=0.00009). The absolute risk reduction was 32%, and the number needed to treat was 3. These results are impressive. The study group is to be commended in the rigorous design and conduct of the trial. This report adds an important contribution of Level 1 evidence to the case series and reports discussed above.

The updated experience in treating radiation-induced proctitis and enteritis from the Virginia Mason group reports a resolution rate of 25% – an improvement of 50-90% in 38%; an improvement of less than 50% in 25%; and an unchanged status in 12% [31].

OTHER ABDOMINAL AND PELVIC INJURIES

In 1978 Farmer and associates [73] reported a single case of vaginal necrosis which resolved with hyperbaric oxygen. In 1992, Williams and colleagues [74] reported their results in treating 14 patients with vaginal necrosis. Thirteen of 14 patients had complete resolution, although one patient required a second course of hyperbaric oxygen. In 1996 Feldmeier and co-authors [75] published their results in a review of 44 patients treated with HBO_2 for a variety of pelvic and abdominal injuries. The results in treating large- and small-bowel injuries were included in the discussion in the section above. Thirty-one patients received at least 20 hyperbaric treatments for radiation injuries to the perineum, groin, vagina and pelvic bone. Twenty-six (84%) of these patients had complete resolution of their radiation injury.

In a recent publication by Fink *et al.* [76], a series of 14 patients treated with HBO_2 for a variety of pelvic injuries is reported. Six of these patients had vaginal injuries (four with ulcers, one with stenosis and one characterized only as vaginitis). Several of these patients had injuries to more than one organ simultaneously. In those treated for vaginal injury either alone or in combination with other injuries, the outcome was complete resolution in one, four with greater than 50% response and one with less than 50% improvement. In the entire group the authors report that 71% had greater than 50% improvement. Most patients received only 30 hyperbaric treatments at 2.4 atm abs.

If we combine the results in these four series including only those with vaginal injury from the Fink paper [76], the combined results show that 45 of 52 (87%) had at least a partial response for miscellaneous radiation injuries to the pelvis – not including cystitis or GI injury, which are discussed above as separate topics.

In a recent review article, Craighead and colleagues [77] from Canadian cancer centers and hyperbaric centers reported their conclusions after conducting a literature search and analysis of two randomized trials and 11 non-randomized trials wherein hyperbaric oxygen was delivered for late radiation injuries after pelvic radiation for gynecologic malignancies. These injuries included radiation-induced cystitis, proctitis and enteritis as well as bone necrosis and quality of life assessments. The authors conclude that HBO_2 is effective for delayed radiation injury especially in the treatment of anal and rectal injuries. The authors further conclude that there is limited but consistent evidence that, when given pre-operatively, HBO_2 has utility in reducing complications in women undergoing surgery within a radiated area to surgically address radiation-induced necrosis.

RADIATION INJURIES OF THE EXTREMITIES

Radiation necrosis of the extremities is a very unusual occurrence. In part, this rarity reflects the relative paucity of primary malignancies of the extremities. However, radiation therapy for bony metastases in the extremities is often delivered. In metastatic disease, radiation doses are only moderate, and patients with metastases may not survive in large numbers long enough for radiation injury to become manifest.

In the review by Feldmeier and Hampson [21] only two publications were discovered which report results of hyperbaric treatment in radiation injuries of the extremities. In 1978 Farmer and associates [73] reported a single patient treated for radiation necrosis of the foot without improvement. Feldmeier *et al.* [78] in 2000 reported a series of 17 patients treated for extremity radiation necrosis. Eleven of 17 patients had complete resolution of their injury with treatment. In those patients for whom follow-up was available and who were not found to have recurrent malignancy in the wound, 11 of 13 (85%) resolved.

Certainly, the published experience in applying hyperbaric oxygen to radionecrosis of the extremities is limited. However, based on the successful treatment of radiation necrosis of both bone and soft tissues in other anatomic sites, it is reasonable to recommend hyperbaric oxygen for this indication.

Oxygen in the hyperbaric setting has often been referred to as a "drug." Just as an antibiotic can be recommended for treatment of an infection of one anatomic site based on success at other sites, we can recommend hyperbaric oxygen for radiation injury of the extremities based on success in other tissues.

Hampson and his co-authors [31] report their results in applying hyperbaric oxygen to soft tissue injuries resulting in cutaneous wounds. These wounds were not limited to the lower extremity. A total of 58 patients were evaluable in this group, with resolution in 26%, 50-90% improvement in 50%, less than 50% improvement in 9% and no improvement in 16%. No patients deteriorated after HBO_2.

NEUROLOGIC INJURIES SECONDARY TO RADIATION

In the review article previously cited, Feldmeier and Hampson [21] have identified 14 publications that report hyperbaric oxygen treatment for a variety of neurologic injuries. These include radiation-induced transverse myelitis (spinal cord injury), brain necrosis, optic nerve injury and brachial plexopathy. Since their review article, a small additional number of papers on this topic have been published.

Radiation myelitis

Radiation myelitis is a very serious but, fortunately, very rare consequence of radiation. Marcus and Million [79] reviewed their experience in the incidence of myelitis in 23 years of treatment of head and neck cancers. They reported an incidence of two patients in a total of 1,112 treated (0.2%). In 1976, Hart and Mainous [54] published their results in the treatment of five cases of transverse myelitis. Glassburn and Brady [80] reported nine cases of transverse myelitis in 1977. In the report by Hart, no improvement in motor function was demonstrated, while in Glassburn's report six of nine patients had improvement, including some improvement in motor function. In 2000 Calabro and Jinkins [81] reported one case of transverse myelitis treated with hyperbaric oxygen who experienced both clinical and MRI imaging evidence of improvement. In a murine study by Feldmeier *et al.* [82], delay but no permanent prevention of myelitis was seen for HBO_2-treated animals administered before objective signs of myelitis seven weeks after a fairly extreme radiation exposure. In another animal model Sminia *et al.* [83] investigated HBO_2 given right after radiation or at intervals of five, 10 or 15 weeks after radiation. Animals had received an initial fractionated dose of 6500 cGy, followed by an additional single dose of 2000 cGy. In this study, animals did not demonstrate radioprotection by the hyperbaric oxygen. The HBO_2 regimen consisted of 30 daily treatments at 2.4 atm abs, each consisting of 90 minutes of 100% oxygen exposure.

No other known successful treatments for radiation-induced myelitis exist, and besides the obvious drastic impact of resultant paralysis, there is a high incidence of mortality in these patients, with two-thirds dying within four years as a result of onset of this condition [84]. Although hyperbaric treatment has not been universally successful because of the severe consequences of transverse myelitis and the total lack of other useful treatments, hyperbaric therapy should be considered on a humanitarian basis for the treatment of radiation-induced transverse myelitis.

Brain necrosis

In the 1976 paper by Hart and Mainous [54] a single case of radiation caused brain injury improved with HBO_2. Chuba and co-workers [85] have reported a series of 10 children with radiation-induced brain necrosis treated with hyperbaric oxygen. All children in this group improved initially. By the time of their publication, four patients had died due to recurrent/progressive tumor, while five of the six remaining patients had maintained their improvement as a result of hyperbaric treatment.

Leber and colleagues [86] have reported two cases where patients developed brain necrosis after radiosurgery procedures for arteriovenous malformations. In both of these patients, the authors report a reduction in the size of necrosis after hyperbaric oxygen therapy demonstrated by imaging studies, and one had complete resolution, as seen by MRI. Cirafsi and Verderamae [87] have published their experience in the treatment of a single case of brain necrosis secondary to radiation. This patient had no improvement with hyperbaric oxygen. The patient had also failed to respond to steroids and anticoagulants.

In a more recent report, Dear and colleagues [88] report that nine of 20 patients with radiation brain necrosis improved with hyperbaric oxygen. Eleven of the patients in this group had glioblastoma multiforme, and only one patient with this diagnosis showed improvement. Since seven of the 11 patients with glioblastoma had died by the time of the report, it is likely that some, if not a substantial part, of their neurologic deficits were the result of tumor as well as radiation injury.

In the largest series to date Gesell and her colleagues [89] have reported the outcome in 29 patients treated with hyperbaric oxygen for radiation-induced brain injury. Objective neurologic exam improved in 58% of these patients, and the need for steroids reduced in 69%.

A problem in the study of these patients is the difficulties in distinguishing radiation necrosis from tumor. Often they occur simultaneously. Necrosis can cause a mass effect and on anatomic based imaging be indistinguishable from a tumor mass. Metabolic imaging with PET scans and MRI spectroscopy can provide useful information, but PET in particular suffers from poor spatial resolution.

When we combine the reports above, we have information on 65 patients who have received HBO_2 for radiation-induced brain injury with improvement in 44 (68%). Again based on humanitarian considerations in the absence of any other effective treatment except surgery, and in consideration of the dire consequences of radiation necrosis of the brain, hyperbaric oxygen should be considered in these instances.

Optic neuritis

A total of four publications reporting the application of hyperbaric oxygen to the treatment of optic neuritis have been published [90-95]. The three case reports demonstrate strongly positive results with hyperbaric treatment while two small case series give mixed but predominately negative results. Borruat *et al.* [93] have reported on a single patient with bilateral optic neuritis. After hyperbaric oxygen treatment, this patient had complete resolution of optic neuritis in the eye most recently affected and some, but less than total, resolution in the first eye affected. This experience supports the need to intervene early with HBO_2. In 1991, Fontanesi *et al.* [92] reported a case of a pediatric patient treated for a CNS tumor. This patient sustained loss of visual acuity, and these changes were refractory to steroids. Hyperbaric oxygen for 20 treatments at 2.0 atm abs each for 90 minutes substantially improved vision in both eyes. Boschetti *et al.* [94], in another case study, report their results in a 41-year-old who sustained visual damage after radiosurgery to the pituitary for Cushing's disease; the damage consisted of blindness in the left eye and temporal hemianopia in the right eye refractory to corticosteroid treatment. After hyperbaric oxygen, blindness persisted in the left eye, but the patient had objective improvement in visual fields in the right eye by formal visual field-mapping. Hyperbaric oxygen consisted of 41 treatments at 2.2 atm abs, each session delivering 60 minutes of 100% oxygen. Guy *et al.* [90], in a series of four patients, report that two who had prompt treatment (within 72 hours of onset) improved, while if treatment was delayed by more than 72 hours, no improvement was detected. In the largest series by Roden *et al.* [91], no improvement occurred in any of the 13 patients treated in this series.

When the results are combined in all of these publications, seven patients in this entire group of 20 (35%) demonstrated improvement with hyperbaric oxygen.

Based on these results, a definitive case for hyperbaric oxygen cannot be made in the treatment of radiation-induced optic neuritis. However, its application here can be supported based on the same mechanisms active in brain necrosis and radiation-induced myelitis. Furthermore, since there are no other known useful therapies and since the prognoses in progressive optic neuropathy – including blindness – are so dire, treatment based on humanistic considerations should be considered. However, these results do show clearly that treatment must be initiated promptly, probably within 72 hours of onset, in order to be effective.

Brachial plexus and sacral plexus

In 1999, a single case report by Videtic and Verkatesan [95] reports a positive resolution of neural symptoms in a patient receiving hyperbaric oxygen for a radiation-induced sacral plexopathy. After treatment, this patient again became ambulatory, and all narcotic analgesics were discontinued.

A randomized controlled trial by Pritchard and associates [96] has been conducted in regard to hyperbaric oxygen therapy for brachial plexopathy. Unfortunately, this trial is negative in terms of failing to show a statistically significant improvement in the hyperbaric group compared to the control group. The median time of entry into the study after development of the neuropathy was 11 years, and the injuries were certainly fixed over time. Though no improvement was observed, the hyperbaric group of patients had less further deterioration than did the control group after treatment. Unexpectedly, six patients with lymphedema in the hyperbaric group showed improvement in their arm swelling after hyperbaric oxygen, with no corresponding improvement in the control group.

SUMMARY FOR NEUROLOGIC INJURIES

The supporting evidence for hyperbaric oxygen for radiation-induced neurologic injury is certainly anecdotal. More study is certainly indicated and justified by the above results. Given the severe and permanent consequences of progression of injury, especially in the CNS and in the complete absence of other effective treatment, serious consideration for hyperbaric treatment should be given.

SPECIAL CONSIDERATION

Hyperbaric oxygen as prophylaxis for radiation injury

Most of the literature cited above reports the results of application of HBO_2 to already expressed radiation injury. A growing body of literature supports the use of HBO_2 in the prevention of radiation injury, usually in the setting of surgery within an irradiated field, where the likelihood of complications is very high.

The first published clinical report investigating prophylactic HBO_2 is that by Marx [32], where hyperbaric oxygen has been shown to decrease the incidence of mandibular osteoradionecrosis from 29.9% to 5.4% when a course of 20 daily HBO_2 treatments was delivered prior to dental extractions from heavily irradiated mandibles. In this protocol, an additional 10 treatments are delivered after extractions to support tissue metabolic demands after surgical wounding. Marx [6] has also reported the benefit of hyperbaric oxygen in the enhancement of osseointegration of dental implants in irradiated bone. Most oral surgeons are reluctant to attempt dental implants in irradiated jaws due to the very high rate of failure and the risk of precipitating osteoradionecrosis. Both Marx [6] and Granstrom [97] have reported the benefit in supporting dental implants in radiated tissues, with significant improvement in osseous integration of the dental implant in patients receiving hyperbaric oxygen. Using the same protocol as for osteoradionecrosis prophylaxis (20 preoperative and 10 postoperative HBO_2 treatments), Marx [6] has achieved an 81% osseointegration success rate, with prevention of osteoradionecrosis in 100% of the patients so treated. A total of 19% failed to osseointegrate as compared to 6% in non-irradiated patients undergoing dental implants. Ueda and colleagues [98] have reported a success rate of 92.3% (in a total of 21 implants) using a similar regimen of HBO_2 in conjunction with dental implants [98].

As already cited above, Feldmeier *et al.* [51] have reported the utility of hyperbaric oxygen in preventing serious wound complications in patients with recurrent head and neck cancer who had salvage procedures, including radical resection within irradiated fields. In that report, 87.5% of patients had prompt wound healing without complication, whereas previous publications report up to a 60% incidence of serious complications in this setting without prophylactic HBO_2. Pomeroy and his associates [99] have reported their results in applying preoperative hyperbaric oxygen as an adjunct to surgery for soft tissue injuries of the pelvis. All five patients in this report had an uneventful postoperative course, although two of five required a second surgical procedure to resolve the radiation injury. In an animal model, Feldmeier and associates have shown the effectiveness of hyperbaric oxygen in the prevention of radiation injury to the small bowel [64,65].

A promising area for clinical application will be the further definition of prophylactic hyperbaric oxygen in the prevention of radiation injury. The development of reliable biochemical predictors of radiation injury would permit the identification of the population at risk for development of radiation injury. At the present time, a reasonable approach is to provide adjunctive HBO_2 when surgery is planned to occur in a heavily irradiated bed. The medical literature is consistent in demonstrating a high rate of serious complications and even death when radical surgical procedures are required in irradiated tissues without prophylactic HBO^2 [50-51]. Third-party insurance carriers must be convinced that such prophylactic intervention is not only valuable for humanistic reasons but also for financial reasons. It is hoped that the literature cited above will provide the individual practitioner with the needed documentation to make a case for the prophylactic application of HBO_2. Hyperbaric oxygen in a preventative setting is likely to be more cost-effective than a prolonged course of rehabilitation and reconstructive surgeries in a corrective fashion.

In summary, the use of hyperbaric oxygen prior to surgery in an irradiated field may prevent or decrease the incidence of catastrophic events such as wound breakdown with bony or hardware exposure, vascular rupture, infection, fistula formation and/or flap loss and prevent further surgical intervention in an already compromised patient.

Concerns related to potential carcinogenesis or cancer growth enhancement

A frequently expressed concern by those considering hyperbaric oxygen for a patient with radiation injury is the fear that hyperbaric oxygen will somehow accelerate malignant growth or cause a dormant malignancy to be reactivated. In Marx's [6] very large group of patients treated with HBO_2 for radiation injury of the mandible, there was no increased likelihood of tumor recurrence or second tumor development. In 1994, Feldmeier and his colleagues [100] reviewed the available literature related to this issue. An overwhelming majority of both clinical reports and animal studies reviewed in this paper showed no enhancement of cancer growth. A small number of reports actually showed a decrease in growth or rates of metastases. Feldmeier [101] updated this material for the Consensus Conference held in 2001 jointly sponsored by the European Society of Therapeutic Radiology and Oncology (ESTRO) and the European Committee for Hyperbaric Medicine (ECHM). In this update, Feldmeier emphasized the differences known in tumor and wound healing angiogenesis, with similar but distinct processes operative in each case. He also showed that there are significant differences

in the growth and inhibition factors, which modulate angiogenesis, in both circumstances. He summarized the literature demonstrating that tumors that are hypoxic are less responsive to treatment, less subject to death by apoptosis and more prone to aggressive growth and lethal metastases. Most experienced practitioners of hyperbaric oxygen no longer fear that hyperbaric oxygen will promote malignant growth

Since the reviews by Feldmeier *et al.*, additional publications have investigated the impact of hyperbaric oxygen on malignancy. Chong and co-workers [102] in 2004 reported their experience in an animal model of transplanted prostate cancer. In this study there was no increase in proliferative index and no increase in tumor vascularity in animals exposed to hyperbaric oxygen *vs.* control animals. Six additional studies have also been conducted on this subject [103-108]. Specific topics studied have included chemically induced mammary tumors in mice, xenografts of human head and neck tumors transplanted in experimental animals and murine colorectal cancer cells implanted to cause liver metastases. All of these papers are negative in terms of observing enhanced tumor growth as the result of hyperbaric oxygen. One paper by Granowitz *et al.* [106] actually shows inhibited growth in a transplanted human mammary tumor.

Lin and collaborators [109] published a retrospective review of 22 patients who underwent salvage surgery for recurrent head and neck cancer after failing primary radiation. Eleven of these patients experienced necrosis and received HBO_2. The other 11 healed without complication and did not receive HBO_2. In the HBO_2 group, nine patients experienced a local failure while in the non-HBO_2 group only four patients sustained recurrence. The authors indicate that all patients were demonstrated to be tumor-free before starting HBO_2 including negative biopsies. The authors suggest that recurrent cancers have a different biology than primary cancers, and while they agree that HBO_2 has not been shown to enhance recurrence of primary tumors, they believe that their results suggest that HBO_2 does likely enhance the re-recurrence rate of salvaged tumors. The numbers are very small, and the groups were not truly matched in that the control group did not experience necrosis. The results could have been just as validly interpreted that necrosis, not HBO_2, enhances re-recurrence.

UTILIZATION REVIEW

Utilization review should be accomplished after 60 treatments when HBO_2 is applied to the treatment of radiation injury. Characteristically, most treatment courses for radiation injury will be in the range of 30 to 60 treatments when the course of treatment is carried out with daily treatments at 2.0 to 2.5 atm abs for 90 to 120 minutes of 100% oxygen.

COST IMPACT

Soft tissue and bony radiation necrosis are fortunately uncommon sequelae of therapeutic irradiation. Approximately 600,000 patients receive therapeutic radiation annually in the United States. The likelihood of serious complications is somewhere between 1-5% of the total, or potentially between 6,000 to 30,000 patients annually. Frequently, these complications require surgery within an irradiated field where the likelihood of significant postoperative complications is on the order of 50%. By either avoiding surgery or supporting surgical healing, HBO_2 therapy can significantly reduce the dollar and human costs of radiation complications. Marx accomplished a dollar cost estimate of the treatment of mandibular osteoradionecrosis [33]. In 1992 U.S. dollars, the cost of måanagement is reduced from about $140,000 when HBO_2 is not utilized to about $42,000 when HBO_2 and surgery are combined in optimal fashion. Similar cost advantages are anticipated in the treatment of radiation injuries of other tissues. ■

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