CHAPTER 8

Delayed Radiation Injuries (Soft Tissue and Bony Necrosis) and Potential for Future Research

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Introduction

The application of hyperbaric oxygen to the treatment and prevention of delayed radiation injury is the core topic for this chapter. A few miscellaneous topics will also be discussed, including areas of interest for research. We will also discuss some of the pertinent literature demonstrating the safety of HBO_2 for the cancer patient. The latest information available from the UHMS in 2019 indicates that delayed radiation injuries are now the most frequent indication for hyperbaric treatments in the United States. The management of delayed radiation injury, especially when bone is involved, requires a multi-disciplinary approach. Importantly, each aspect of treatment, including technique when surgery is needed, must be optimized to give the best chance for a successful therapeutic effort. In the pages that follow, 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. Recently, there have been several negative articles for hyperbaric oxygen in the management or prevention of mandibular necrosis. Many of these articles are limited in value since they either include patients who are at low risk for ORN after extractions because of any of the following: they were treated only to moderate doses of radiation; or the teeth extracted were outside the region of high radiation dose deposition; or they were maxillary teeth. With previous radiation techniques we would say outside the radiation field, but given the complexity of modern radiation planning, these areas might not be totally outside a combination of many beamlets that are employed in intensity modulated radiation therapy (IMRT), the common standard targeted therapy for head and neck cancers. Many in the radiation oncology community have predicted much lower incidence of radiation injury as the consequence of image-guided targeted techniques including IMRT.[1] It has not yet been firmly established that IMRT will deliver a lower incidence of ORN and other serious radiation complications at various sites.

In the treatment of osteoradionecrosis (ORN), other recent papers question the need for HBO_2 and instead advocate for microvascular surgery and free flaps when treating a Marx Stage III ORN patient who requires a segmental resection and reconstruction. See below for a more extensive discussion of these topics within the specific sections dedicated to them.

The Nature of Radiation Injury

Radiation injuries should be classified as acute, subacute or delayed complications.[2] Acute injuries are due to direct and essentially immediate cellular toxicity caused by free radical-mediated damage to DNA in normal cells surrounding the tumor. Many cells suffer a mitotic or reproductive death, i.e., enough damage has been rendered to the DNA that successful subsequent cell division and reproduction are prevented. This mechanism is felt to be the primary method by which most cancer cells are destroyed.[3] In normal tissues, these acute injuries occur most notably in rapidly dividing cells such as those lining the GI tract from mouth to anus.[4] These injuries are seen frequently in the oral and pharyngeal mucosa. Acute injuries to normal tissues are typically self-limited and almost invariably resolve within a few weeks of completing the course of radiation. They rarely persist beyond two months. Treatment

is generally symptomatic providing nutritional support and pain control. Though self-limited, the acute injuries can be very debilitating throughout their duration and must not be neglected. 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 with onset between 8 to 12 weeks post radiation. When this syndrome occurs, it is termed radiation pneumonitis. Subacute injuries also occur in the spinal cord as the result of temporary demyelinization. The so-called Lhermitte's sign is caused by this damage.[5] In this syndrome, patients experience electric-like shocks (paresthesias) down their legs with spinal extension (forward bending). Subacute effects, too, are most often self-limited but on a rare occasion evolve to become delayed injuries. Some subacute injuries may persist for several months. Treatment is symptomatic. No specific treatment is especially effective although steroids are commonly employed. Supplemental oxygen may be required for patients with radiation pneumonitis. Delayed radiation complications are typically seen after a latent period of six months or more and may rarely develop many years after the radiation exposure.[4,6] Sometimes, especially when chemotherapy and radiation are given as combined modality treatment, acute injuries are so severe that they never resolve and evolve to become chronic injuries indistinguishable from other delayed radiation injuries.[7] Harmful effects evolving in this fashion 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 trauma or surgery within the radiation field. On the other hand, frequently late radiation injuries are spontaneous, and no immediate precipitating insult or injury can be identified.

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.[8] Considerations of cost (both direct and indirect) would have to be considered along with efficacy in any hyperbaric intervention for these injuries because they almost always resolve with supportive care.

The Etiology of Delayed Radiation Injury

The exact causes and physical and biochemical processes leading to delayed radiation injury are complex and still only partially understood.[9] They continue to be studied.[4] In virtually all instances which demonstrate late radiation damage, we observe vascular changes characterized by obliterative endarteritis.[6,10-11] Because hyperbaric oxygen has been shown to enhance angiogenesis in hypoxic tissues, the hyperbaric oxygen community has traditionally postulated that the enhancement of angiogenesis is the primary therapeutic effect of hyperbaric oxygen in radiated tissues. Some radiation scientists are now convinced that at least in some organ systems, vascular changes play only a minor role in the evolution of delayed radiation injury and instead radiation-induced apoptosis and exuberant fibrosis are the predominant causes of delayed radiation injuries.[12]

Therefore, 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, suggesting that the mechanisms of injury were unrelated. Indeed, it is not uncommon to find a patient with serious acute reactions who does not suffer late complications or someone with severe delayed complications who had experienced no worse than minor acute radiation reactions. Radiation researchers now appreciate that the process of radiation injury is initiated at the time of radiation treatment and involves the elaboration and release of many bioactive substances prominently including fibrogenic cytokines.[13] The process whereby therapeutic radiation inflicts delayed damage on normal tissues has been recently described as the fibroatrophic effect by Delainian and associates.[12] This model emphasizes the consequences of the observed depletion of stem cells and subsequently parenchymal cells. It also highlights the exuberant fibrosis found in severely damaged irradiated tissues. 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 not felt by this group to contribute significantly to delayed radiation injury, at least as a primary cause.

It has been demonstrated that chronically hypoxic tissues are subject to exuberant fibrosis mediated by HIF-1.[14] It is very likely that the fibrosis that is generated in radiated tissues is at least a partial consequence of radiation-induced vascular damage and consequent tissue hypoxia.[15] It is also likely that exuberant fibrosis seen in radiated tissues also is at least a partial causative factor of subsequent vascular damage by "squeezing out" or compressing small vessels.

A recent review of the mechanism of delayed effects of radiation has been accomplished by Fleckenstein et al.[13] The author of this paper focuses on delayed radiation injuries of the lung. This paper identifies TGF-beta as the most frequently studied cytokine associated with radiation injury. Additional cytokines associated with radiation injury include IL-1 (Interleukin-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. The increase in these cytokines begins at the time of radiation, but the damage caused may take months or even years to be clinically expressed.

Many studies of cytokines and radiation injuries have been accomplished in animal models of radiation-induced pneumonitis.[16] To date, we have not been able to make practical clinical application of these observed associations, either as a predictor of or therapy for radiation injury. No single marker is likely to provide us with a reliable estimate of future radiation damage.[13] Similarly, no practical strategies have yet been developed to prevent or reduce the production of these cytokines or reduce their impact in a preventive fashion. We know that there is a very wide range of tolerance to radiation by individual patients based on heterogenous genetic makeup and that some patients are much more sensitive to radiation injury.[17] If reliable predictors of delayed radiation injury were available during or before treatment, adjustments to the radiation dosing and targeting scheme could be made for the radio-sensitive patient. Some exquisitely sensitive patients might be advised to seek alternative therapies (if available) instead of radiation if indeed these determinants reliably predict severe complications. Moreover, prophylactic interventions such as hyperbaric oxygen or other yet-to-be studied or applied pharmacologic interventions could be given before or during the latent period, i.e., before the manifestation of the chronic injury. Drugs that have shown promise to mitigate radiation injuries include antioxidants, free radical scavengers, inhibitors of apoptosis, anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, growth factors, and cytokines.[9,18] 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 severity. Obviously, this premise will have to be subjected to clinical trials, and the most important consideration would be to do nothing that jeopardizes tumor control, i.e., do nothing that protects the tumor as well as normal tissues from radiation damage.

A similar intent (the prevention of radiation damage) led to the development of the Marx 20/10[19] protocol prior to dental extractions in heavily radiated patients (doses over 6000cGy) to prevent the clinical expression of mandibular necrosis, when not only the mandible itself but also the surrounding soft tissues suffer damage. This damage might be subclinical at that time. This group of patients will also have had significant compromise in the soft tissue of the head and neck surrounding the mandible that can be mitigated by HBO_2.

The Effects of Hyperbaric Oxygen on Irradiated Tissues

The impact of hyperbaric oxygen in terms of its beneficial effects is likely to involve at least three mechanisms in radiation damaged tissues:

1. Hyperbaric oxygen stimulates angiogenesis and secondarily improves tissue oxygenation.
2. Hyperbaric oxygen reduces fibrosis.
3. Hyperbaric oxygen mobilizes and induces an increase of stem cells within irradiated tissues that can differentiate, as needed, by that tissue.

Because a consistent manifestation of radiation injury is vascular damage and resultant hypoxia, the known impact of hyperbaric oxygen in stimulating angiogenesis continues to be an obvious and important mechanism, whereby hyperbaric oxygen is effective in radiation injury. HBO_2 induces neovascularization in hypoxic tissues. A recent animal study by Deschpande and colleagues[20] demonstrates a significant and quantifiable reduction in irradiated vasculature in rat mandible following irradiation. Marx[21] has demonstrated both the prehyperbaric oxygen vascular damage and the enhanced vascularity and cellularity in heavily irradiated tissues after hyperbaric oxygen therapy by comparing histologic specimens from patients pre- and posthyperbaric oxygen. Marx[21] 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[21] in an animal model of irradiated rabbit mandibles with angiography have shown increased vascularity in mandibles after exposure to hyperbaric oxygen. Svalestad and associates[22] demonstrated in a controlled human study of irradiated patients employing Doppler flow studies and transcutaneous oxygen measurements that patients after HBO_2 had improved blood flow and improved tissue oxygen content as measured by serial transcutaneous measurements. Johnson-Arbor and her associates[23] have published a case report employing indocyanine green fluorescent angiography in a patient treated for breast necrosis and was shown to have a region of poor vascularity at the site of the injury that showed improved vascularity with HBO_2.

In fibrosis as one of the elements of radiation, Feldmeier and his colleagues[24-25] 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, which stains collagenous materials blue.

Many head and neck cancer patients sustain woody fibrosis of the soft tissues of the neck after a full course of radiation.[26]The authors have personally observed and other clinicians have noted significant reduction in this woody fibrosis of soft tissues of the neck following a course of hyperbaric oxygen intended to treat mandibular necrosis. To our knowledge, this effect has not yet been systematically studied, and it is not readily apparent in all patients but is a frequent finding.

The hyperbaric study group headed up by Dr. Thom[27-28] while at the University of Pennsylvania has published studies demonstrating the mobilization of stem cells mediated through nitric oxide with HBO_2. These papers include an animal model as well as 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 demonstration of increased cellular density in histologic preparations from patients initially demonstrating hypocellularity after hyperbaric oxygen for mandibular osteoradionecrosis.[21]

Hyperbaric oxygen has been applied as a therapy for delayed radiation injury for more than 40 years.[29-30] Hyperbaric oxygen as a neoadjuvant treatment prior to dental extractions is also supported by a randomized controlled trial and several other case series. The following sections will discuss 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)

One of the earliest and most frequently applied applications for hyperbaric oxygen in late and chronic radiation injury is its utilization 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.[29-30]

The likelihood of mandibular necrosis as a result of therapeutic radiation varies widely among several reports. During the era of mostly cobalt therapy and before IMRT, Bedwinek[31] 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[32] estimated a 5% incidence when a small portion of the mandible (less than one-third) is irradiated to 6500 cGy or higher and a 5% incidence at 6000 cGy or higher when a larger volume of the mandible is irradiated. Reuther and associates[33] at the University of Heidelberg in a 30-year review of 830 patients reported an 8.2% incidence of ORN and interestingly also reported resolution in only 40% of their patients of which the vast majority were managed conservatively. The current application of IMRT has been predicted to reduce mandibular radiation necrosis compared to older radiation techniques.[1,34] These referenced studies show that the volume of mandible included within the high dose volume is an important determinant of the occurrence of ORN. Recent publications of a now mature experience with IMRT are demonstrating an incidence of 7 to 10% of ORN in the IMRT era.[35-36] Besides the wide adoption of IMRT for head and neck cancers, an even more drastic change has been the adoption of primary radiation with chemotherapy sensitization as initial treatment for most head and neck cancers. Radical surgery is saved as an option for salvage of persistent or recurrent tumor.[37] This change in philosophy has increased radiation doses from 5,000 to 6,000 cGy as an adjuvant treatment to doses of 7,000 cGy or higher as curative primary doses. Chemotherapy, given often to act as a radiosensitizer, would be expected to increase normal tissue damage as well as enhance control of the malignancy.

Not all cases of exposed mandibular bone after radiation are ORN. It has been reported that 85% or more of cases resulting in initially exposed mandibular bone will resolve spontaneously with conservative management.[38] Unfortunately, when the exposed bone persists, the remaining cases generally become chronic and progressive. When ORN develops, it is typically accompanied by considerable insult to the surrounding soft tissues as well as bone. A useful impact of HBO_2 is to enhance the quality of soft tissues that surround the necrotic bone and, in this way, indirectly support its resolution.

Much of the early work in this area considered radiation-induced mandibular necrosis to be a subset of mandibular osteomyelitis. At the USAF Hyperbaric Medicine Center in San Antonio, there was an initial experience in delivering HBO_2 often along with antibiotics as treatment for mandibular necrosis without surgical management and after failure of more conservative therapy.[39] Although most cases would show temporary improvement including alleviation of the characteristic pain of ORN with HBO_2 as monotherapy, virtually all cases of moderate to severe ORN would recur if hyperbaric oxygen was administered without appropriate surgical debridement or resection.

Dr. Robert Marx, DDS. and his colleagues[21,39-40] elucidated many fundamental principles in the etiology and management of mandibular ORN which have led to a rationale approach to its management. Dr. Marx 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.[39] Consistent with Marx's elucidation of the pathophysiology of mandibular ORN, it is appropriate to think of ORN as an avascular necrosis.[39] Since a major goal in applying hyperbaric oxygen is to enhance the vascular milieu, the bulk of the hyperbaric oxygen in his protocols is given prior to surgical wounding including dental extractions.[21] In this fashion, the normal soft tissues are conditioned to better deal with the stress and increased metabolic demand of surgical wounding. Marx has also shown that

for hyperbaric oxygen to be consistently successful, it must be combined with surgery in an optimal fashion. The surgical procedures have evolved over the years with the advent of microvascular free flaps and other technical improvements including the use of adjuncts in bony reconstruction, but the importance of adjunctive HBO_2 has not changed and is still essential in Dr. Marx's experience.[21]

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.[21] Note: There are other staging systems, but none has shown any clear superiority to the Marx system.[21,41]

Marx Stage I ORN: This stage includes those patients with persistently devitalized 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 for months or they have rapidly progressive ORN. These patients begin treatment with 30 HBO_2 sessions followed by relatively 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.

Marx 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 they receive a more radical surgical debridement or resection in the operating room followed by 10 postoperative treatments. This surgery is often an en bloc resection of the alveolar ridge. Surgery for Stage II patients must maintain mandibular continuity. If mandibular segmental resection is required, patients are advanced to Stage III and require reconstruction.

Marx 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 in 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 from its initiation. 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 postresection treatments. At this surgery, this group of patients may require soft tissue enhancing procedures including free flaps or myocutaneous flaps.[21] Typically, after a period of about three months, the patients complete a reconstruction, which may involve various surgical techniques. 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 2019, microvascular free flaps are frequently used, most often employing an autologous fibula. 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. Also, typically in the current version of the protocol, at the time of the resection a customized titanium tray is placed internally to maintain the anatomic and functional relationships of the mandible until the formal reconstruction is accomplished. In Marx's hands currently, cancellous bone is obtained by aspiration with a trocar from the ilium and that bone along with several adjuvants including growth factors, bone morphogenic protein and platelet rich plasma are combined in a cocktail and inserted into the mandibular deficit to complete the bony reconstruction. [21]

Marx[21] has recently reported his updated results in 914 patients treated according to the above protocol. In his hands with this technique, successful resolution has been achieved in 100% of patients. Unfortunately, the vast majority of patients require treatment as Stage III patients necessitating mandibular resection and reconstruction.[42] Dr. Marx has always sought cosmetic restoration as well as the success in supporting a denture. These two issues, cosmesis and restoration of dentition for mastication, are necessary components in improving quality of life in this group of patients.[43] In fact, Dr. Marx[21] has established six criteria for a successful mandibular reconstruction in an ORN patient requiring mandibular segmental resection:

1. Restoration of Jaw Continuity
2. Restoration of Alveolar Height
3. Restoration of Alveolar Width Suitable for Dental Implants
4. Restoration of Arch Form
5. Maintenance of Bone
6. Restoration of Facial Contours

Feldmeier and Hampson[44] 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 very 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 (ATA) or 2.0 ATA. The paper states that those treated at 2.0 ATA "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.,[45] failed to report a positive outcome in applying hyperbaric oxygen to the treatment of mandibular ORN. In this paper, 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. Of note was how readily the Marx protocol was adopted and transferred successfully in both the academic and private practice setting as employed by those authors reviewed in this section of the Feldmeier-Hampson paper.[44]

Since that review, several additional papers have been added to the literature. A paper not included in the 2002 systemic review by Feldmeier and Hampson comes from Freiberger[46] and associates at Duke University. The authors of this publication report a high resolution or response rate of 88% with mean duration of 86.1 months of follow-up in their patients in non-smokers. Nine of their 57 patients receiving HBO_2 had recurrent malignancy. Forty-one of this group of 57 had ultimately failed previous treatment.

A multi-institutional randomized controlled trial by Annane et al.[47] 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. Patients were randomized to receive either 90 minutes of 100% O_2 at 2.4 ATA or a breathing gas mix delivering an equivalent partial pressure of oxygen 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 multi-disciplinary 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 three decades earlier, Marx[40] had shown an absolute necessity of surgically eradicating all necrotic bone. The need to remove all necrotic bone to achieve resolution was also confirmed by Feldmeier et al.[48] in their earlier report of chest wall necrosis including some cases with ORN of the ribs and sternum.

Additional criticisms of this study by Annane have been made. Moon et al.[49] have shown that nearly two-thirds of the hyperbaric group received fewer than 22 hyperbaric treatments. Laden[50] 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 ATA. Mendenhall,[51] a prominent 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. Interestingly, he also remarks that it is hard to understand why the HBO_2 group in the Annane study did worse than control.

In another paper subsequent to the Feldmeier and Hampson[44] review paper, Gal and associates[52] have published their results in treating a series of 30 patients with Marx Stage III mandibular ORN with debridement and often segmental resection and reconstruction employing microvascular anastomosis for free flaps. 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 had undergone some debridement prior to coming to Gal. Once in the author's hands, they all had appropriate debridement or resection of all necrotic bone 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 of 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, in these patients those principles previously established by Marx, i.e., an emphasis on presurgical hyperbaric oxygen and debridement of all necrotic bone followed by reconstruction with postoperative hyperbaric oxygen, were not adhered to. 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.

In a 2017 publication by Dielman et al.,[53] the authors present their recommendations for treatment of ORN based on experience with 27 patients with ORN out of 509 evaluated (5.3%) radiated patients in a retrospective review. They continue to recommend hyperbaric oxygen for Stage I and II ORN, but recommend primary surgical intervention for Stage III consisting of segmental resection and a free flap reconstruction without HBO_2. Hyperbaric oxygen is recommended in Stage III when there is extensive soft tissue damage or other complications which are not well delineated by the authors.

A series of papers from several centers beginning in 2008 and extending to 2018 recommend free flap reconstructions after resection of necrotic bone, including segmental resection of the mandible without hyperbaric oxygen for Stage III mandibular necrosis.[54-56] Their success rate in re-establishing mandibular continuity was on average approximately 85%. However, serious complication rates are on the order of 50%. In one report, re-operation is required in about 60% of patients. In these papers, dental rehabilitation with implants when reported was only accomplished on the order of 7 to 10%. Free flap patients characteristically require one or two days' care in an ICU and continued hospital-care thereafter for a week or more.

Teng and Futran[57] have also 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 fibro-atrophic model of radiation injury as now dominant in the opinion of many experts of radiation pathology.

Dr Sylvie Delainian,[58] a French radiation oncologist who has been the major proponent of the fibro-atrophic model of delayed radiation injury, has published several papers advocating a medical treatment for late radiation injuries including ORN. The protocol consists of pentoxifylline (800mg), Vitamin E 1000 IU) and clodronate (a bisphosphonate) (1600mg) daily Monday through Friday. On Saturday and Sunday, the patients receive prednisone (20mg) and ciprofloxacin (1000mg). Most notably she and her colleagues have completed and published a Phase II trial applying this treatment to 54 patients.[58] Thirteen of these patients are said to have failed HBO_2. Twenty-five patients had undergone surgical intervention previously. These patients were treated for 16±9 months. She reports complete response in all patients in a median time of nine months. She also reports that two-thirds of her patients were Stage III disease by the Epstein scale with fistula, fracture or "osteitis." Nearly one half (24) of these patients had only 1mm of exposed bone. The authors do state that the lesions were fairly minimal in extent with the average length of exposed bone 17±8mm. Thirty-six of these patients required "iterative sequestrectomies." Eight patients are reported to have nondisplaced fractures. Fifteen of 54 patients stopped their medical therapy early, and six of 54 or 11% of patients died of sepsis attributed to local severe infection, fistula or mandibular fracture progressing to cellulitis and sepsis. The authors considered even those patients who had exposed bone of up to 5 mm length at the completion of PENTOCLO treatment as "complete responders!"

These results are quite interesting and need to be confirmed in a randomized trial. Dr. Delianian[59] suggests that the medical combination therapy she advocates for ORN may have broad applicability to delayed radiation injuries of many organs and tissue types. She does advocate randomized controlled trials to confirm its routine use.

Hampson et al.[60] 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. Several publications advocate no hyperbaric oxygen and instead fibular free flaps for mandibular reconstruction following segmental resection of Stage III ORN of the mandible. [53-55] As previously noted, these procedures have a high complication rate and rarely allow for dental rehabilitation with dental implants.

Advocates of this technique point out that patients are planned for a single surgery to resect the necrotic bone and accomplish the reconstruction. In part, they argue that patients are eager to have the surgery done in a single stage because they are impatient. Yet, these patients have been dealing with a chronic problem typically at least for several months, and are not likely to be too impatient at this point as long as they are seeing progress toward resolution. The free flap procedures typically require a hospital stay of several days or a week, and for the first day or two require intensive care. The procedure is quite expensive, especially when the required in-patient stay is considered. Per Dr. Marx, the cost is more than $90,000 per patient and increases even more if the patient must be returned to the operating room to relieve flap congestion, remove a venous clot or repair the anastomosis. These needed returns to the operating room occur from 5%-25% of patient reconstructions.

Only one of these recent publications (The Annane Study) was a randomized controlled trial, and it is subject to the criticisms in design as discussed above. If we look at the total body of literature reporting the impact of hyperbaric oxygen on mandibular ORN, we find that the publications reviewed in the Feldmeier/Hampson analysis,[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[21] studies, resolution is noted in 100% of cases and he has now reported on the treatment of 914 patients. Marx also indicates that success in Stage III patients requires not only re-establishment of mandibular continuity but also rehabilitation including the six criteria listed in the text above. The Freiberger[46] paper demonstrates a positive durable outcome in 86% of their 65 patients. By contrast, if we look at the recent trials not employing HBO_2, only 22 patients are included in the Gal report[28] and 31 patients randomized to hyperbaric oxygen in the Annane study.[47] The Delainian[58] Phase II study reported results in 54 patients.[57] Those papers reported above by Hirsch, Nolen and van Gemert employing free flap reconstruction for ORN, the numbers of patients studied in the respective publications were 21, 89 and 79 respectively. Practitioners of hyperbaric oxygen who treat mandibular ORN must do so in a multidisciplinary manner and ensure that treatment includes a reconstructive surgeon who can and will 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.

Neoadjuvant HBO_2 Prior to Dental Extractions

Extraction of teeth from heavily irradiated jaws is a common precipitating factor for mandibular necrosis. In roughly one half of cases of ORN of the mandible, extractions or some other surgery is the precipitating event. The rest are spontaneous and may develop several to many years after the radiation.[33] Marx[19] 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 versus penicillin prophylaxis. Those patients assigned to the hyperbaric group completed 20 pre-extraction daily HBO_2 treatments with ten additional postextraction 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 ORN was more pronounced in the penicillin group with nearly three-quarters (8/11) requiring treatment as Stage III patients. Neither patient with ORN from the hyperbaric group required a resection with reconstruction and both resolved with treatment as Stage II 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 presurgical/pre-extraction hyperbaric oxygen to improve tolerance to surgical wounding including the soft tissues surrounding the mandible. Extraction technique is also very important in radiated patients. Many recommend that extraction sockets be closed, and a careful alveoloplasty should be accomplished to prevent any prominent or sharp bony prominences. Several reports recommend against elevation of the mucoperiosteum unless absolutely required. 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. There are several additional positive case series reporting outcome in applying hyperbaric oxygen prior to dental extractions. Dr. Paul Lambert and associates[61] from Dayton, OH, VA Medical Center report their series of 47 evaluable patients who underwent HBO_2 in support of dental extractions following the Marx protocol. No ORN occurred following these extractions. In the publication of Vudiniabola et al.[62] following the Marx protocol in ORN prophylaxis, one of 29 patients experienced ORN while in a similar case series from David et al.,[63] one of 24 patients experienced mandibular ORN after extractions from a radiated mandible following the prophylactic application of hyperbaric oxygen. Another publication is the report of 40 patients by Chavez and Atkinson[64] in whom hyperbaric oxygen was applied in the

manner prescribed by Marx (20 pre-extraction hyperbaric treatments followed by 10 postextraction). The authors report that uncomplicated healing of tooth sockets was observed in 98.5% of extractions. In the recent review by Hampson et al.,[60] 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, 100% were felt to have a major response and 92% had no evidence of ORN.

An even larger experience comes from the latest update of Marx's[21] results in extracting teeth in high risk patients. In this update applying the 20/10 protocol for over 30 years in high-risk patients, he reports a 0.75% incidence of ORN in 936 patients involving the extraction of 2,019 teeth.

Sulaiman et al.[65] 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 cases (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. In this group of patients one half of the teeth extracted were outside the radiation field. Marx's patients in his prophylactic study all had teeth extracted from within the radiation fields and had doses of 6800cGy or greater while in the Sulaiman report 68% received doses lower than 6900 cGy. Twenty-one percent received doses less than or equal to 5900 cGy. Twenty percent of patients had extractions of anterior teeth, likely outside the radiation treatment ports.

Other authors have likewise presented series of patients in whom hyperbaric oxygen was not used pre-extractions and ORN incidence was low. In all these papers, groups of low-risk patients were included, including extractions of maxillary teeth, anterior mandibular teeth outside the radiation field and patients who received low total radiation doses. In the paper by Makkonen et al.[66] from 1986, i.e., before the IMRT era, the authors report the results in 25 patients who had a total of 94 teeth extracted after radiation and found no cases of ORN. However, this group included many low-risk patients. Six patients had maxillary tooth extractions. Eleven were lymphomas, and the median radiation dose for this group was only 4,100 cGy. Of the 66 mandibular extractions, 47 were either incisors or canine teeth, i.e., anterior teeth outside the typical radiation fields.

In another paper from 1991, Maxymiw et al.[67] from Princess Margaret, the group reported 72 patients with 449 teeth extracted. This group of patients was largely a low-risk group: median radiation dose less than 5,000 cGy, only 44% of teeth were within the radiation field and 44% of the teeth were in the maxilla.

In 2007 Lye and co-authors[68] reported another series of 40 patients undergoing a total of 155 extractions without HBO_2 and prospectively followed and evaluated for delayed healing and ORN after radiation. Patients were classified as demonstrating normal healing, delayed healing or ORN. Those patients exhibiting delayed healing were 5.8% of the total and those developing ORN was 1.9%. This report also included a sizeable number of low-risk patients. Forty-one percent were maxillary teeth, and another 23% were anterior mandibular teeth likely outside the radiation field.

Dr. Lewis Clayman[69] published a review paper in 1997 stating the data didn't support mandatory use of HBO_2 before removing teeth in irradiated mandibles." As a review paper, the publication included no original data. Dr. Clayman presents a series of articles in which patients with low risk for ORN are key to his conclusions. These include the papers by Makkonen[66] and Maximiw,[67] which are discussed above pointing out their inclusion of low-risk patients, including those with low doses, teeth outside the radiation portals and maxillary teeth. Dr. Clayman

recommends that extractions be done by dentists experienced in dealing with irradiated patients and that they utilize careful technique.

Michael Wahl,[70] a dentist in private practice, published a review article in 2006 in the most prominent radiation oncology journal. Many of the papers included in his review are subject to the same criticisms applied to the Clayman paper. No new data were presented in this paper. In this review, he concluded there was not sufficient evidence to support the use of prophylactic HBO_2 treatments before extractions or other oral surgical procedures in radiation patients.

Again, in evaluating the literature both positive and negative for peri-extraction HBO_2 in support of dental extractions, we must look carefully to the details of the publication. When high-risk patients are included, the publications recorded above do indeed support HBO_2 with the intent of extracting teeth without triggering the onset of ORN; whereas, patients in a low-risk status do not benefit from HBO_2 to support their dental extractions. In order to sort out which patients are in the high- versus low-risk categories, the hyperbaric physician must obtain the radiation records and ideally discuss the case with the treating radiation oncologist given the complexity of modern IMRT-based radiation treatment planning.

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%. [71-72] 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 even if there is no recurrent or persistent malignancy, there are no effective therapies to reverse necrosis.[73] 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. Aggressive biopsies and the resultant surgical wounding of already injured tissues may further exacerbate tissue damage.

Chandler[74] has established a system to grade the severity of laryngeal necrosis. Most with Grade 1 and 2 levels of necrosis will resolve with conservative treatment. Patients suffering from Grade 3 or 4 necrosis are very likely to require laryngectomy. Five institutions have now published case series in applying hyperbaric oxygen to the treatment of radiation laryngeal necrosis.[60,75-78] Additionally, a new single case report has also been published.[79] In the earlier reports, most patients were treated for severe laryngeal necrosis (Chandler Grade 3 or 4). The outcome in a total of 44 cases is reported and only six patients were failures to treatment and required total laryngectomy.[75-79] The other 38 patients maintained their voice box and most ultimately had good voice quality.

In the recent very large case series of multiple different sites of radiation injury assessed prospectively and reported by Hampson et al.,[60] there were 27 patients treated and evaluable for soft tissue necrosis of the larynx. Improvement by at least 50% was seen in 82% of these patients. Twenty patients were retrospectively graded by the Chandler's system described above, and 18 of 20 were advanced Grade (Chandler's Grade 3 or 4). All but one of these patients improved by at least one Chandler's grade and 11 improved by two or more Chandler's grades. Two patients completed HBO_2 at a Grade 3 or 4 and likely progressed to laryngectomy although that information was not provided in the manuscript. In the case report by Hsu et al.,[79] their patient with Chandler's Grade 4 had complete resolution after 40 hyperbaric oxygen treatments.

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 Whelan-Kindwall *Hyperbaric Medicine Practice 4th Edition* textbook, Dr. Marx[21] has reported extensive experience in treating soft tissue radiation injuries of the head and neck. In a controlled, randomized report of 240 patients requiring flaps (pedicled or free flaps) to repair soft tissue damage or replace surgically removed or damaged soft tissues, he has compared wound infection, dehiscence and delayed healing in a hyperbaric group receiving the 20/10 protocol versus a control group. He found that HBO_2 patients experienced 11% wound infection versus 37% control; 6% dehiscence versus 26% control; and 14% delayed wound healing versus 46% control respectively in HBO_2 vs non-HBO_2 patients. All differences are statistically significant with a P value equal to 0.005.

Like results have also been reported by other authors. Davis and his colleagues[80] 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[81] 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. No serious bleeds occurred in the hyperbaric group.

In another group of patients, Feldmeier and colleagues[82] have reported in abstract form the successful adjuvant treatment of patients undergoing radical surgical resection for salvage of recurrent or persistent head and neck cancer following full course prior irradiation. Serious surgical complications, including occasional fatalities, have been reported to occur in over 60% of patients undergoing radical cancer salvage surgery within a previously irradiated field without the benefit of HBO_2.[83-84] 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.

Miscellaneous Soft Tissue Injuries of Head and Neck Cancer Patients: A Potential as Preventive Treatment and to Enhance Quality of Life (QoL)

Head and neck cancer patients are now being cured in about two-thirds of cases. Radiation therapy is a mainstay of this curative treatment. An interesting new promising application for hyperbaric oxygen is an application to head and neck cancer patients soon after radiation to ameliorate acute radiation injuries and improve quality of life.

Gerlach and associates[85] accomplished a quality of life prospective study on a group of 21 head and neck patients receiving hyperbaric oxygen for either prevention or treatment of ORN. The patients received hyperbaric oxygen between four months and five years after completion of their radiation. The hyperbaric exposure was 85 minutes of 100% oxygen at 2.5 ATA for a total of 30 to 40 treatments with the majority given before any surgical procedures much like the Marx 20/10 and 30/10 protocols. Radiation doses varied from 5,000 to 7,000 cGy. The patients completed a subjective questionnaire before HBO_2 and at one and two years post-HBO_2. A European

Organization for Research and Treatment of Cancer questionnaire was employed to compare several parameters of quality of life (QoL). The questionnaire was completed before HBO_2 and at 12 and 24 months post-HBO_2. The authors report improvement in swallowing, subjective improvement in volume of saliva and improvement in taste at both follow-up time intervals. At 24 months, swallowing problems had decreased by 23%, the subjective perception of saliva had improved by 13%, and subjective improvement in taste had improved by 22%. Subsequent to this study, Teguh and colleagues[9] have conducted a small randomized trial of 19 patients where the study group of patients immediately following a full course of radiation received 30 hyperbaric treatments at 2.5 ATA for 90 minutes. These investigators also employed a quality of life questionnaire from the European Organization for Research and Treatment of Cancer. Improved outcomes for these patients compared to control included improved swallowing, improved quality and quantity of saliva and decreased oral pain.

These reports are certainly promising and warrant further investigation. While we make progress in the control of cancer, QoL issues have become all the more important and are rightfully the topic of frequent study in the oncology community. The discussion above in developing biochemical predictors of the severity of effects of treatment on the individual cancer patient might allow us to intervene early in a group of patients found to have a high likelihood of significant diminishment in QoL based on a reliable predictor or group of predictors or clinical considerations such as re-irradiation after an initial failure. While it is probably not fiscally possible to offer all cancer patients a course of HBO_2 to result in an improved Qol and it is unlikely that this entire group would be willing to subject themselves to HBO_2 after a long and rigorous course of oncologic treatment, it may be possible and appropriate to offer this therapy to a subset of patients at high risk for these long-term effects of treatment that will decrease their enjoyment of the years of life provided by modern aggressive oncologic treatments. Here, too, the promise of this type of treatment must be established by additional quality research.

Chest Wall Necrosis

Radiation therapy after lumpectomy has become the preferred treatment for most early breast cancers.[86] After this treatment, fat necrosis of the intact breast has been reported but is an uncommon clinical problem. Radiation therapy is frequently used as an adjuvant treatment following mastectomy in more advanced cancers for large tumors, when axillary metastases are present or if it is the patient's preference. When a patient is irradiated after mastectomy, the radiation dose to the skin is not designed to provide a skin dose sparring effect because the treatment is designed to cover the dermal lymphatic vessels which may harbor microscopic metastases. As a result of this standard radiation technique, most women irradiated after mastectomy are subject to brisk acute radiation reactions including inflammation, brisk dermatitis, sometimes ulceration and accompanying pain. Some patients experience large areas of moist desquamation accompanied by superficial ulceration during and just after radiation treatments. 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 ensure a vascular supply which is unimpaired by radiation vascular injury.

As early as 1976, Hart and Mainous[29] 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[87] 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 patients who were cancer-free and suffered only soft tissue necrosis were treated successfully. However, only eight of 15 patients who also had ORN of the ribs or sternum achieved resolution. The common characteristic in these failed cases was the failure to surgically eliminate 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.

Carl and Hartmann,[88] then from the University of Düsseldorf in 1998, reported a single case of a patient who had experienced long-standing, painful breast edema following lumpectomy and postoperative radiation. After 15 daily hyperbaric treatments of 90 minutes of 100% hyperbaric oxygen at 2.4 ATA, the patient experienced complete resolution of pain and edema.

In a second publication, Carl and his associates[89] in 2001 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 telengectasias 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 LENT-SOMA score, (Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic), a validated and often applied system for grading radiation damage.[90] 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 telangectasia/erythema. Only patients with at least grade 3 pain (persistent and intense) or a summed LENT-SOMA score of at least 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 LENT-SOMA scores in women receiving treatment compared to those who did not; however, in this study fibrosis and telangiectasia were not reduced. All 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.

Teguh and associates[91] reported a group of 57 prospectively followed women who suffered late radiation damage and symptoms after breast conserving treatment. Their symptoms and response are as follows: For severe pain in the arm and shoulder prior to HBO_2 46%, post-HBO_2 17%; for swollen arm and hand prior to HBO_2 14%, after 7%; for difficulty in lifting arm or moving it sideways before HBO_2 45%, after 22%; for pain in the breast before HBO_2 67%, after 15%; for swelling in breast 45% before HBO_2, after 13%; for hypersensitivity of the breast before HBO_2 54%, and after 15%; for abnormal skin changes in the breast before HBO_2 32% and after 11%. Symptoms were reduced by two-thirds in most categories and at least one-half in the rest.

Enomoto and colleagues[92] reported in 2017 a case of a 74-year-old woman who 25 years after adjuvant radiation following mastectomy to her chest wall and lymphatics developed a chronic draining skin ulcer with undermining and a fistulous tract. She was reported to also have "osteomyelitis" of the ribs. More likely this was ORN. She completed 101 HBO_2 treatments consisting of 100% oxygen at 2.5 ATA with complete resolution.

Radiation Cystitis

Radiation therapy is commonly delivered to tumors of the pelvis including 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[44] in a 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.[93] was the largest series. It was a prospective but nonrandomized and noncontrolled trial. All 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. When we combine all of the patients from these 17 papers, we find that 76.3% of 145 patients resolved with HBO_2.

Since this review article, there have been additional reports of hyperbaric oxygen for radiation cystitis. Neheman et al.[94] 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 ATA 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, the recurrent 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 publication from 2003 Corman et al.,[95] the authors report a series from Virginia Mason of 57 patients in 2003 treated for radiation cystitis with HBO_2. Chong et al.[96] have updated this series in 2005 with an additional three patients. In this report, the average number of treatments was 33 at 2.36 ATA 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 publication by Chong et al.[96] discussed above, the authors report the importance of early intervention. In their analysis, they have 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.

In a third publication from this group, results in the hyperbaric treatment of 411 patients with various radiation injuries treated at the Virginia Mason Hyperbaric Medicine Section between 2002 and 2010 are reported. Hampson et al.[60] report 44 evaluable cases treated for radiation cystitis. In this group, the average number of treatments was 42. Fifty-seven percent achieved complete response and another 32% improved from 50 to 90%. No patients receiving HBO_2 demonstrated progression during the period of follow-up.

A very recent review article was accomplished in 2018 by Cardinal et al.[97] The authors selected 16 papers for inclusion. These papers reported the results on 602 patients with radiation-induced cystitis of whom 84% had at a partial or complete response. Recurrences were reported in 10 of the papers included in this review where 12-month follow-up was available. Fourteen percent recurred at time intervals between three and 120 months (median 10 months).

Hemorrhagic cystitis is often a serious and not uncommonly a life-threatening disorder. Cheng and Foo[98] 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 cystectomy and 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 Li and colleagues,[99] the authors report a 3.7% mortality rate in their review of 378 patients experiencing hemorrhagic cystitis. All these patients had been irradiated for cervical cancer.

In summary, the vast majority of published series applying hyperbaric oxygen to radiation cystitis are positive reports. This success rate is especially noteworthy when compared to those publications cited above highlighting a poor outcome and significant mortality rate when HBO_2 is not administered, even when radical surgical intervention is employed. Also, many of those reporting HBO_2 for radiation cystitis identify a significant recurrence rate in spite of a good initial response. Hampson has reported an average of 40 or more treatments in the treatment of radiation cystitis and has also noted the importance of early intervention. Several authors report a second course of HBO_2 for those with recurrence and that in most cases they also report a positive response. The authors

of this chapter have experienced a group of patients who may require 60 or more treatments to achieve durable resolution and believe that it is reasonable to offer patients more than the typical number of 40 HBO_2 treatments recommended in radiation injury elsewhere as long as these patients continue to demonstrate response but still have significant evidence of ongoing radiation damage. It is also reasonable to offer patients a second course of hyperbaric oxygen therapy if they recur after a positive response to an initial course of therapy.

Radiation Proctitis and Enteritis

For the most part, radiation enteritis and proctitis have been addressed together in previous publications. In regard to their incidence, a paradox exists. The small intestine is known to be more sensitive, i.e., subject to damage at lower radiation doses, but the colon and especially the rectum are more frequently injured in clinical practice. This seeming contradiction occurs because modern targeted radiation techniques are much more successful in avoiding the small bowel. Whereas, the large bowel, because much of it is in a fixed position in the retroperitoneum and because it is usually in much closer proximity to tumor sites in the prostate, uterus, uterine cervix or even the rectum itself, more commonly receives a potentially damaging radiation dose.

An animal study has been reported by Feldmeier and associates[24-25] 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. Animals were euthanized seven months after the radiation exposure. Both gross and histologic morphometry were accomplished and demonstrated a statistically significant reduction in signs of enteritis in the experimental group compared to the radiation only control group. Additionally, both quantitative histologic morphometry and a mechanical stretch test demonstrated significant reduction in submucosal fibrosis and an increase in mechanical compliance for hyperbaric treated animals.

In the review by Feldmeier and Hampson from 2002,[44] nine clinical papers reporting the results of hyperbaric oxygen in the treatment of enteritis or proctitis had been 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. Four percent of patients had no benefit from treatment.

A case report by Neurath and colleagues[100] 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 ATA for 90 minutes.

Since the systematic review of 2002, additional papers on this topic have been published. Jones et al.[101] have reported 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 these 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. One patient discontinued treatment after the chamber facility at which he was being treated had been closed for an extended time due to concerns related to potential SARS exposure. Two patients 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 showing durability.

In another series from Girnius et al.[102] 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.

The Virginia Mason group has published their previous experience with radiation-induced proctitis and enteritis in two publications.[103-104] 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 (4 stomach, 7 small bowel, 6 colon and 6 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 ATA for 90 minutes of 100% O_2. In those patients demonstrating a partial response at this point, additional treatments were delivered (6 to 30 treatments). Complete overall response rate 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 more proximal lesions.

In a randomized, controlled, double-blinded trial sponsored by the Baromedical Research Foundation, Clarke et al.[105] have reported their results in applying hyperbaric oxygen to patients with refractory chronic radiation-induced proctitis. One hundred fifty patients were enrolled in the trial, and 120 were evaluable. Patients were assessed utilizing the LENT-SOMA scoring systems which have become standard in studies of radiation injuries/complications. Patients in the active arm were treated on 100% at 2.0 ATA. Sham patients were exposed to very slightly elevated pressures (1.1 ATA) breathing air. The intent was to accomplish blinding of the control patients by giving them a 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. Ultimately, 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 one1 year), those patients in the active arm showed a statistically increased improvement in their LENT-SOMA 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 three. These results are impressive. The researchers are 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.

An updated experience in treating radiation-induced proctitis and enteritis from the Virginia Mason group is included in their general review of the treatment of radiation injuries from 2002 to 2010. For enteritis and proctitis, this 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%.[60] It is likely that some patients had been reported in earlier papers from this same group.

Glover and co-investigators[106] in 2015 reported the results of a randomized, double-blinded controlled trial investigating HBO_2 for radiation proctitis. Eighty-four patients were randomized (55 to hyperbaric treatment and 29 to a sham control). The hyperbaric profile consisted of a total of 40 exposures at 2.4 ATA, five days per week, for 90 minutes of 100% oxygen at pressure over eight weeks' time. The investigators had two major endpoints for the study: change in the inflammatory bowel disease questionnaire (IBDQ) and change in rectal bleeding score. These metrics were determined for each patient at initiation of treatment, at two weeks post-treatment and 12 months post-treatment. No significant changes were detected in either measure at these follow-up points.

Several criticisms have appeared in print relative to this study. These include their reports of some patients with minimal symptoms, the employment of the IBDQ which was designed to follow patients with inflammatory bowel problems not radiation injury, and the long duration of proctitis before entering into the trial (a median of 43 months).

The American Society of Colon and Rectal Surgeons published their clinical practice guidelines for the treatment of chronic radiation proctitis in 2018.[107] In this paper, they define the problem of chronic radiation proctitis, discuss systemic and topical chemical and pharmacologic interventions, including oral mesalamine, formalin instillation and sucralfate enemas, as well as review physical measures such as argon plasma coagulation, electrocoagulation and radiofrequency ablation. They also discuss hyperbaric oxygen and reference several publications. In this review and in the formulation of their guidelines, they determine that HBO_2 is a class 1B indication, i.e., it is strongly indicated based on moderate quality evidence.

Other Abdominal and Pelvic Injuries

In 1978 Farmer and associates[108] reported a single case of vaginal necrosis, which resolved with hyperbaric oxygen. In 1992, Williams and colleagues[109] reported their results in treating 14 patients with vaginal necrosis. Thirteen of 14 patients had complete resolution, although one responding patient required a second course of hyperbaric oxygen. In 1997 Feldmeier and his co-authors[110] published their results in a review of 44 patients treated with HBO_2 at 2.4 ATA for 90 minutes for a variety of pelvic and abdominal injuries. Forty-one were available for follow-up. Six patients had necrotic wounds in the groin. Four of these healed and two were not available for follow-up. Two patients were treated for pelvic bone necrosis. One healed after 48 treatments. The other refused additional treatments after just five treatments and did not respond. Seven had perineal wounds. Three of these had complete healing. Two had inadequate treatment. One was lost to follow-up, and one did not heal. Five had vaginal necrosis and all healed. Another 16 had cutaneous nonhealing wounds of the abdominal wall and will be discussed in the section on skin injury below. Eight had bowel injuries and were already included in the section above on bowel injury.[44] Thirty-one of these patients in all categories 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. Of note was the subset of eight patients with rectovaginal or rectovesical fistulae. In this group, six resolved and three of these did not require surgical intervention. Two did not resolve. Closure of fistulae after radiation is an especially difficult problem generally requiring major surgical excisions and reconstructions employing omental flaps, and even with these interventions, the failure rate is high.

In a more recent publication by Fink et al.,[111] 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 including the vaginal injuries and other sites within the pelvis, the authors report that 71% had greater than 50% improvement. Most patients received only 30 hyperbaric treatments at 2.4 ATA.

In a review article, Craighead and colleagues [112] along with authors from several Canadian cancer centers and several hyperbaric centers reported their conclusions after conducting a literature search and analysis of two randomized trials and 11 nonrandomized trials. In these publications, hyperbaric oxygen was delivered for late radiation injuries after pelvic irradiation 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 HBO_2 has utility in reducing complications in women undergoing surgery within a radiated area to surgically address the radiation-induced necrosis.

Miscellaneous Cutaneous Radiation Injuries

In the review by Feldmeier and Hampson,[44] only two publications were discovered which report the results of hyperbaric treatment in radiation injuries of the skin, mostly in the lower extremities. Farmer and associates[108] in 1978 reported a single patient treated for radiation necrosis of the foot without improvement. Feldmeier et al.[113] in 2000 reported a series of 17 patients treated for radiation necrosis involving the lower extremity. One lesion was a combination of bone and soft tissue necrosis. The rest were cutaneous lesions, i.e., skin necrosis. Five of these were at least 10 cm in the greatest dimension. Eleven of 17 patients had complete resolution of their injury with treatment. If we restrict our review to patients in whom follow-up is available and who were not found to have recurrent malignancy, eleven of 13 or 85% resolved.

In the paper by Feldmeier et al.[110] previously described in the section above discussing miscellaneous pelvic and abdominal injuries, 15 lesions involved skin of the anterior abdominal wall. With adjuvant hyperbaric oxygen, eight healed, four did not heal and three had an inadequate course of HBO_2. A course of therapy was considered inadequate when the patient had fewer than 20 hyperbaric treatments.

In the paper from Virginia Mason reporting 411 radiation injuries at multiple sites, fifty-eight patients who were available for follow-up had skin lesions.[60] The authors report 26% complete response and another 50% who had between 50 to 90% response.

In those anatomic sites mentioned above, especially the patients with breast or chest wall damage, much of the radiation damage involved skin and the discussion for these sites as well as the publications discussed in this section are pertinent to the application of HBO_2 to radiation skin damage including necrosis and ulceration.

Neurologic Injuries Secondary to Radiation

In the review article previously cited, Feldmeier and Hampson[44] 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 this review article, additional papers on this topic have been published.

Radiation Myelitis

Radiation myelitis is a very serious but fortunately very rare consequence of radiation. It results in paralysis and is essentially a functional cord transection caused by radiation. Marcus and Million[114] reviewed their experience in the incidence of cervical spinal 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[29] published their results in the hyperbaric treatment of five cases of transverse myelitis. Glassburn and Brady[116] reported nine cases of transverse myelitis in 1977 treated with HBO_2. 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. Calabro and Jinkins[117] in 2000 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.,[118] delay but no permanent prevention of myelitis was seen for HBO_2 treated animals administered before objective signs of myelitis at seven weeks after a fairly extreme radiation exposure. In fact, the authors discuss that in the study design, the radiation exposure created a 100% incidence of myelitis where an incidence of 50% had been predicted for the control group. Sminia et al.[119] in another animal model investigated HBO_2 given right after re-irradiation of rat spinal cords or at intervals of 5, 10 or 15 weeks after the first cycle of radiation. Animals had received an initial fractionated dose of 6,500 cGy followed by an additional single dose of

2,000 cGy one year after the first course of radiation. In this study, animals did not demonstrate radioprotection by the hyperbaric oxygen. The HBO_2 regimen consisted of 30 daily treatments at 2.4 ATA, each consisting of 90 minutes of 100% oxygen exposure.

Feldmeier and associates[121] have reported a single case report in 2009 at the UHMS annual meeting. In this case a 51-year-old woman with multiple myeloma after two stem cell transplants and other aggressive chemotherapy along with spinal radiation from vertebral levels T-8 to T-12 developed neurologic deficits consisting of a Brown-Sequard pattern with motor and sensory loss on opposite sides of the body. She had weakness, including foot drop in her right lower extremity with back pain and paresthesias in her left lower extremity. Spinal MRI was consistent with radiation myelitis. She completed 40 hyperbaric treatments at 2.5 ATA for 90 minutes of 100% oxygen at pressure. At the completion of treatment, she had improvement in motor and sensory deficits including resolution of her foot drop and was able to undergo physical therapy for rehabilitation. It should be noted that this successful treatment was offered to a patient who was not suffering from a complete loss of neurologic function in her spinal cord, i.e., the cord had not withstood a complete loss of function due to the radiation. Also, of note is that a post-HBO_2 MRI showed resolution of spinal cord damage when compared to the pre-HBO_2 images which were consistent with radiation myelitis.

Other than HBO_2, 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 this condition's onset.[122] Although hyperbaric treatment has not been universally successful, because of the severe consequences of progressive 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. Treatment should be initiated as soon as possible to enhance the likelihood of a therapeutic response.

Brain Necrosis

In the 1976 paper by Hart and Mainous,[29] a single case of radiation caused brain injury improved with HBO_2. Chuba and co-workers[122] have reported a series of 10 children irradiated for primary brain tumors with radiation-induced brain necrosis who were treated with hyperbaric oxygen. All children in this series improved initially. At 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[123] have reported two cases where patients developed brain necrosis after radiosurgery procedures for arteriovenous malformations. In both of these patients, the authors report clinical improvement and a reduction in the size of necrosis by imaging after hyperbaric oxygen therapy. One had complete resolution by MRI. Neither patient required steroids. Cirafsi and Verderamae[124] have published their experience in the treatment a single case of radiation-induced brain necrosis involving the brainstem. This patient had no clinical improvement with hyperbaric oxygen or steroids or anticoagulants. Interestingly three years after HBO_2, the lesion was not visible by MRI.

In a more recent report, Dear and colleagues[125] report that 9 of 20 patients with radiation brain necrosis improved with hyperbaric oxygen. Eleven of the patients in this group had been irradiated for glioblastoma multiforme and only one patient with this diagnosis showed improvement. Since 7 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 and patient deterioration, were the result of tumor as well as radiation injury.

Gesell and her colleagues[126] in the largest series to date 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 recurrent or persistent tumor. Often, they occur together. 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.

In a systematic review of toxicities, Fetcko and colleagues[127] report the pooled results of 29 studies. In this report they discovered a range of radiation necrosis incidence of from 0 to 33% after stereotactic radiosurgery with a pooled average of 6.5% for newly diagnosed high-grade gliomas. For recurrent gliomas treated with radiosurgery, the incidence increases to as high as 44% in one study.

There are few effective treatments for brain necrosis. Surgical resection is an option if the site affected is a "non-eloquent" region of the brain and accessible to surgery. Avastin, which is a VEGF inhibitor, has been found to reduce vascular permeability and in this way reduce perilesional edema.[128] A multi-institutional nonrandomized study employing Avastin (bevacizumab) has been reported to have achieved its primary goal of reducing perilesional edema by at least 30% in 78.9% of patients at three months, but only 42% of patients had an improvement in performance status.[128] In consideration of the dire consequences of radiation necrosis of the brain and the success reported in the case series cited above (60 to 70% improvement), in these instances, based on humanitarian considerations and the absence of other effective options, hyperbaric oxygen should be recommended in these patients on a case by case basis.

Radiation-Induced Optic Neuritis

A total of seven full publications and one letter to the editor addressing the application of hyperbaric oxygen to the treatment of optic neuritis are summarized here.[129-136] Borruat et al.[129] 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.[130] have reported a case of a pediatric patient treated for a CNS tumor who sustained complete loss of visual acuity, and these changes were refractory to steroids. Hyperbaric oxygen for 20 treatments at 2.0 ATA each for 90 minutes substantially improved vision in both eyes. Boschetti et al.,[131] in another case study, reported their results in a 41-year-old patient who sustained visual damage after radiosurgery to the pituitary for Cushing disease, consisting of blindness in the left eye and temporal hemianopsia 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 ATA each delivering 60 minutes of 100% oxygen. Guy et al.,[132] in a series of four patients, report that two who had prompt treatment (within 72 hours of onset) improved, but if treatment was delayed by more than 72 hours, no improvement was detected. These authors contend that unless HBO_2 is initiated early after onset of visual loss, no improvement will be experienced. In the largest series by Roden et al.,[133] no improvement occurred in any of the 13 patients treated in this series. In a letter to the editor commenting on the Roden publication, Guy[134] expresses several criticisms of this paper. Guy points out that none of the patients in Roden's series had HBO_2 treatment within two weeks of onset and sometimes the interval was as long as 12 weeks. He also points out that Roden's patients were treated at 2.0 ATA whereas his patients were treated at 2.8 ATA. Guy also observes that Roden's publication included only central visual acuity and no visual field mapping was done.

Malik and Golnik[135] report four consecutive patients with optic neuritis. Two of the patients had bilateral involvement and the other two unilateral. The patients with bilateral involvement had preservation of the vision in the eye less affected. These two patients in their more affected eye, and the two patients with unilateral involvement experienced progressive loss of vision after HBO_2. Their patients were also treated with steroids.

Li and associates[136] published a single case report of the application of HBO_2 to a patient with optic neuropathy. The patient was a 78-year-old who had an initial course of 30 HBO_2 treatments with some improvement. She had improvement in vision and returned to being able to ambulate, but then deteriorated and had 40 more HBO_2 treatments with repeated favorable response. She ultimately failed the HBO_2 with permanently impaired vision. She did have MRI studies pre- and post-HBO_2 that gave radiographic evidence of resolution in spite of ultimate clinical deterioration.

Overall, in the above publications, seven patients had improvement with HBO_2 while 18 (including the one patient who had temporary response) had progressive visual loss. Thirteen of these nonresponders came from the Roden publication wherein all patients had a delay of at least two weeks from onset of visual loss to start of HBO_2. 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 humanitarian considerations should be considered. These results also clearly show that treatment must be initiated promptly, probably within 72 hours of onset, in order to be effective. HBO_2 treatment at 2.4 ATA may be more effective than lower pressures.

Brachial Plexus and Sacral Plexus

In 1999, a single case report by Videtic and Verkatesan[137]reports 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[138] 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 we would expect that the injuries were fixed over time. Though no improvement was observed, following treatment the patients who had received HBO_2 had less deterioration than did the control group. Unexpectedly, six patients in the hyperbaric group with lymphedema showed improvement in their arm swelling after hyperbaric oxygen with no corresponding improvement in the control group.

Summary for Neurologic Injuries

Time from onset of symptoms until intervention for these disorders must be minimized to increase the likelihood of response. 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 essentially a complete absence of other effective treatment in almost all instances, serious consideration for hyperbaric treatment should be given.

The authors recommend treatment at 2.4 ATA with a minimum of 40 treatments in almost all circumstances. Additional treatments can be considered according to patient response.

Special Considerations

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[19] 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. 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[21] and Granstrom[139] 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 has achieved an 84% osseointegration success rate with prevention of osteoradionecrosis in 100% of the patients so treated. Granstrom, in his review article of 2006 summarizing the results of 38 publications, has reported a failure rate of 13.5% when peri-implant hyperbaric oxygen has been employed compared to a 21.4% failure rate in radiated jaws without hyperbaric oxygen. Ueda and colleagues[140] 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.

As already cited above, Feldmeier et al.[82] 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[141] 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 small bowel.[24-25]

A promising area for clinical research 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.[82,142] Third-party insurance carriers must be convinced that such prophylactic intervention is not only valuable for humanitarian reasons but also for financial reasons. We would actually propose that such therapies should be thought of as neoadjuvant therapies in the same way that radiation or chemotherapy are often delivered in a neoadjuvant fashion to optimize surgical outcome prior to exploration and attempted surgical resection of a tumor. When hyperbaric oxygen is employed, pre-extraction or pre-surgical reconstruction or other surgeries in a heavily radiated field more than six weeks after the radiation, the radiation-induced vascular and fibroatrophic changes are well on their way to expression in those tissues about to be subjected to the stress of surgical wounding. It is hoped that the literature cited above will provide the individual practitioner with the needed documentation to make a case for the neoadjuvant

application of HBO_2. Hyperbaric oxygen in a preventive 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 as a neoadjuvant treatment 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. More formalized study of this potentially important application of HBO_2 should be accomplished to establish the specific protocols for and instances in which HBO_2 would offer an important decrease in complications and even death.

Hyperbaric Oxygen as a Hypoxic Cell Radiosensitizer

The classic works by Gray[143] and Churchill-Davidson[144] led to over three decades wherein hyperbaric oxygen was employed as a radiation sensitizer in thousands of patients in mostly randomized and controlled studies. Gray and colleagues[143] had shown in the laboratory in 1953 that well-oxygenated cancer cells are as much as three times more sensitive to radiation cell kill as are poorly oxygenated cells. Many cancers are well known to harbor high percentages of hypoxic cells. Churchill-Davidson,[144] in an extraordinary instance of translational research in 1955, reported enhanced tumor response in treating malignant lung masses in eight patients. Half of each mass was treated in air and the other half in oxygen while compressed in the chamber. Enhanced tumor response was demonstrable in three-quarters of the patients treated when breathing hyperbaric oxygen. Although even in retrospect the many studies that followed showed significant improvement in local tumor control and survival in selected cases, this practice of simultaneous hyperbaric oxygen and irradiation has largely disappeared. However, beginning with brain tumors, several Japanese investigators have subsequently demonstrated significant increased tumor response by exposing patients to hyperbaric oxygen and then irradiating them.[145-146] As long as the time interval between hyperbaric treatment and radiation does not exceed 15 minutes, the improvement in tumor response is quite impressive. Measurements employing implanted Eppendorf electrodes have shown that in head and neck cancers, the increased oxygen tensions in the tumor persist for up to 25 minutes in some patients after they are removed from the chamber.[147] The persistence of this enhanced oxygen continues to render the tumor cells more susceptible to cell kill by the increased oxygen tensions. High-grade brain tumors are a good model in some ways for these studies because local control of the tumor is usually indicative of a cure since these tumors rarely metastasize outside the CNS. However, since these tumors have a high lethality rate, even significant improvement in response is unlikely to result in a higher cure rate. It may prolong patient survival. A Phase 1 dose escalation study has now been completed and published in 2017 wherein head and neck cancer patients underwent a 30-minute hyperbaric exposure at 2.4 ATA and then were taken immediately to the radiation suite and had their daily dose of radiation within 15 minutes of leaving the chamber.[148] Twelve patients were enrolled and 9 were evaluable. These patients had oropharyngeal primary cancers and had Stage IVA or IVB disease. They received standard radiation (7,000 cGy over seven weeks) along with weekly Cisplatin chemotherapy at 30mg/m^2. Now with five-year follow-up, these nine patients demonstrate 100% five-yr survival, 0% local recurrence and one patient (11%) with distant metastases. These results are much better than historic controls but admittedly, this is a small number of patients in an uncontrolled trial. Efforts are being made to launch a randomized Phase 3 trial at this time.[149]

Another interest that has arisen over the last 10 years or so is the combination of a ketogenic diet (KD) and hyperbaric oxygen as a treatment strategy for cancer treatment. For a number of years, the ketogenic diet has been a subject of interest in cancer care.[150] When patients eat a low carbohydrate, high-fat diet, it is believed that increased metabolic oxidative stress is created for the cancer cell, resulting in increased cancer cell death. Cancers have been known for years to preferentially use non-aerobic glycolysis or fermentation rather than oxidative

phosphorylation for energy production.[151] Otto Warburg[151] won the Nobel Prize for demonstrating that tumors prefer anerobic pathways of glycolysis even when oxygen is available. A recent animal study investigating the combination of HBO_2 and the ketogenic diets to treat metastatic disease has been published.[152] The results were very impressive, resulting in nearly an 80% increase in survival of treated vs control mice. Very limited clinical experience with this approach is published. The clinical experience of combined hyperbaric oxygen and KD consists of a single case of a patient with metastatic breast cancer treated for metastatic breast cancer along with hyperthermia.[153] The postulated mechanism for combined KD and HBO_2 is the following:

1. KD diet weakens cancer cells by sugar deprivation and anti-cancer effects of ketone bodies leading to protective effect for non-cancerous cells, which can metabolize ketones.
2. KD sensitizes cancer cells to HBO_2 created ROS and oxidative damage.[152]

While promising in very preliminary research, the concept of combining KD and HBO_2 in the routine treatment of cancer has inadequate support as yet to recommend except in clinical trials. Certainly, larger, well-designed clinical studies must be accomplished before it can be routinely recommended.

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 re-activated. At first glance, this concern seems reasonable and even intuitive since hyperbaric oxygen is often given to enhance cell and vascular growth in the chronic wound. In Marx's[21] very large group of patients followed by him and treated with HBO_2 for radiation injury, there was no increased likelihood of tumor recurrence or second tumor development. Marx has reported a 28.5% rate of recurrence in the hyperbaric patients versus a 30.8% in 390 patients he has followed who have not had HBO_2. In 2003, Feldmeier and his colleagues[154] reviewed the available literature related to this issue. An overwhelming majority of both clinical reports and pre-clinical studies reviewed in this paper showed no enhancement of cancer growth. A small number of reports actually showed a modest decrease in growth or rates of metastases in animal models. In this review, the authors emphasized the differences known in tumor and wound healing angiogenesis with similar but distinct processes operative in each case. They also showed that there are significant differences in the growth and inhibition factors, which modulate angiogenesis, in both circumstances. They summarized the literature demonstrating that tumors that have a large fraction of hypoxic cells are less responsive to treatment, less subject to death by apoptosis and more prone to aggressive growth and lethal metastases.

Two other well-done review articles have been subsequently published. Daruwalla and Christophi[155] in 2006 in their review concluded that most of the literature indicated HBO_2 did not have an impact on tumor growth, whether stimulatory or inhibitory. In a third comprehensive review by Moen and Stuhr,[156] these authors concluded there was no evidence indicating that HBO_2 acted as a stimulator of tumor growth or as an enhancer of recurrence.

In addition to the reviews by Feldmeier et al., Daruwalla et al. and Moen et al., additional publications have investigated the impact of hyperbaric oxygen on malignancy. Chong and co-workers[157] 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 versus control animals. Another six studies on this subject have shown no enhancement of tumor growth or likelihood of cancer recurrence.[158-163] Specific topics studied have included the impact of hyperbaric oxygen on 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 these papers are negative in terms of observing enhanced tumor growth as the result of hyperbaric oxygen. One paper by Granowitz et al.[161] actually shows inhibited growth in a transplanted human mammary tumor.

A few publications have been reported to demonstrate enhanced growth or recurrence of cancer. Eltorai and colleagues[164] in 1987 report three cases of urothelial tumors that developed in patients who had received hyperbaric oxygen and also had indwelling urinary catheters for a prolonged period of time. Bradfield and co-authors[165] report a series of four head and neck cancer patients who appeared to have rapid progression of their cancers after exposure to HBO_2. Two of these patients had locally advanced (T4) cancers at presentation. Another had a long interruption of his radiation, and long breaks in a course of radiation are known to decrease the effect of treatment. The authors of this paper recommend further investigation.

Lin and collaborators[166] 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 following the salvage surgery and received HBO_2. The other eleven healed without complication and did not receive HBO_2. In the HBO_2 group, nine patients experienced a local cancer recurrence while in the non-HBO_2 group only four patients sustained recurrence at the time of the publication. It should be noted that follow-up in this group of 22 patients was as short as 12 months. 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. In the hyperbaric patients in this group, the five-year disease-free survival was 32.7%. In a review paper combining the results in 16 studies and including 729 patients undergoing salvage surgery in head and neck cancers without hyperbaric oxygen, the five-yr overall survival rate was 37%.[167]

Most experienced practitioners of hyperbaric oxygen no longer fear that hyperbaric oxygen will promote malignant growth, and now that cancer patients are living longer with their malignancy, it is not uncommon and not inappropriate in the opinion of the authors to offer patients with active malignancy HBO_2 when they present with radiation injuries or other appropriate indications for a course of compassionate use hyperbaric oxygen therapy.

Utilization Review

Utilization review should be accomplished after 60 treatments when HBO_2 is applied to radiation injury. Characteristically, most courses for radiation injury will be in the range of 30 to 60 hyperbaric treatments when the course is carried out with daily treatments at 2.0 to 2.5 ATA for 90 to 120 minutes of 100% oxygen. The Marx rabbit mandible study and the authors' experience suggest that 2.4 ATA is the preferred pressure for treating radiation injuries. Dr. Marx[21] recommends that when patients are treated with HBO_2 for radiation injuries at 2.0 ATA, the hyperbaric oxygen exposure be increased from 90 to 120 minutes.

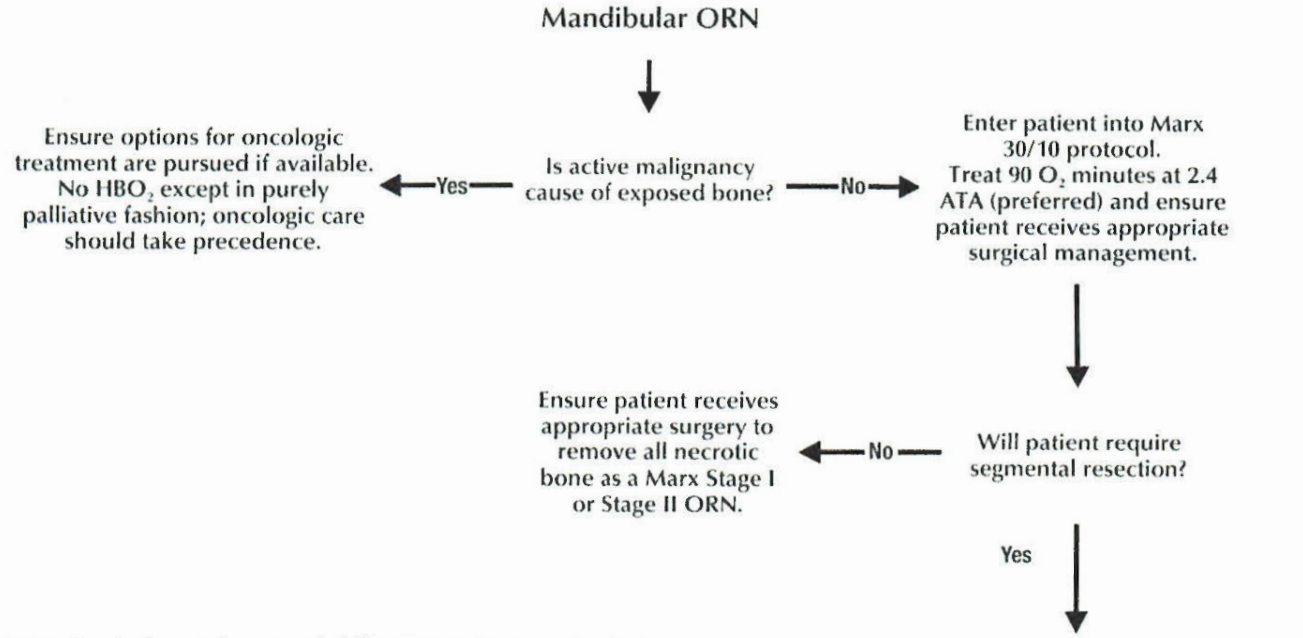
Cost Impact

Soft tissue and bony radiation necrosis are fortunately uncommon sequelae of therapeutic irradiation. Approximately 700,000 patients receive therapeutic radiation annually in the U.S. The likelihood of serious complications

is somewhere between 1 to 5% overall but can range up to 25 or 30% in some applications. 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. Dr. Marx[21] has updated his dollar cost estimate of the treatment of mandibular osteoradionecrosis. In 2016 U.S. dollars, the cost of management is reduced to about $96,000 when HBO_2 is utilized according to the Marx protocol compared to about $224,000 when HBO_2 is not employed. Similar cost advantages are anticipated in the treatment of radiation injuries of other tissues. These estimates do not include indirect costs such as days of missed work for the patient or supporting family members.

Flowcharts for Management of Delayed Radiation Injuries
Details of management are described in the text.

Figure 1.



Note: Surgical experience and skills play an important role in accomplishing a successful course of treatment. Reconstructive surgery may take several forms including free flaps, when soft tissue is also needed. To complete reconstruction, pedicle flaps or free flaps may be appropriate.

This flowchart, though referring to mandibular ORN, with slight modification, may be applied to ORN at other anatomic sites.

Figure 2.

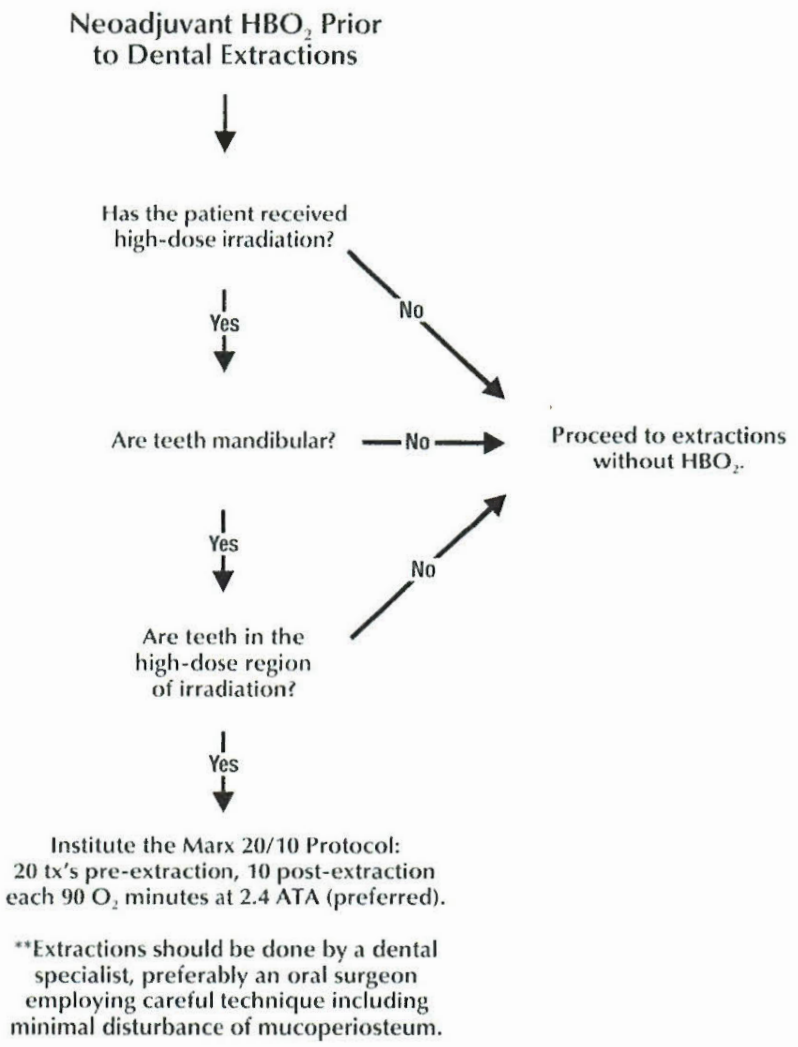


Figure 3.

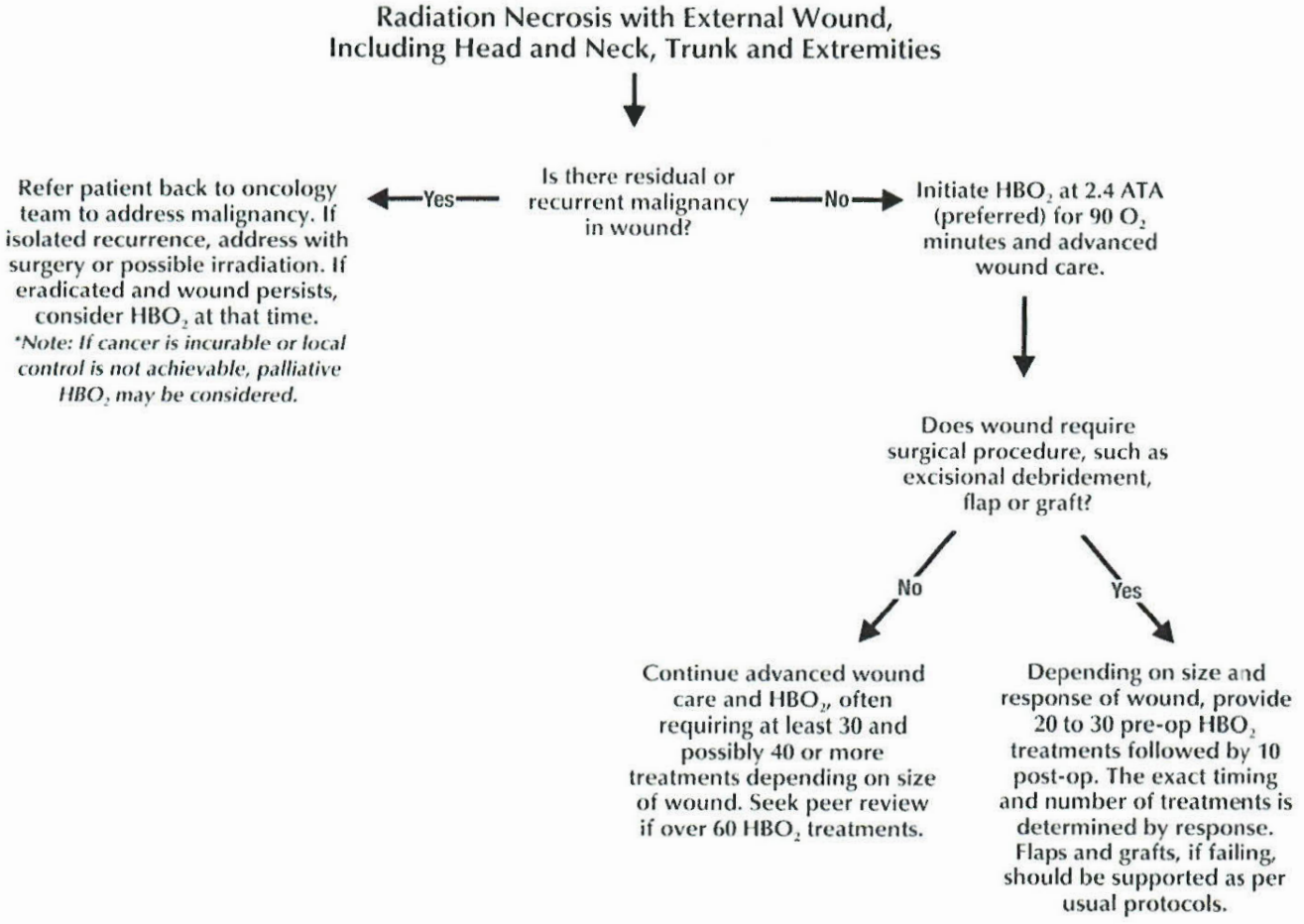


Figure 4.

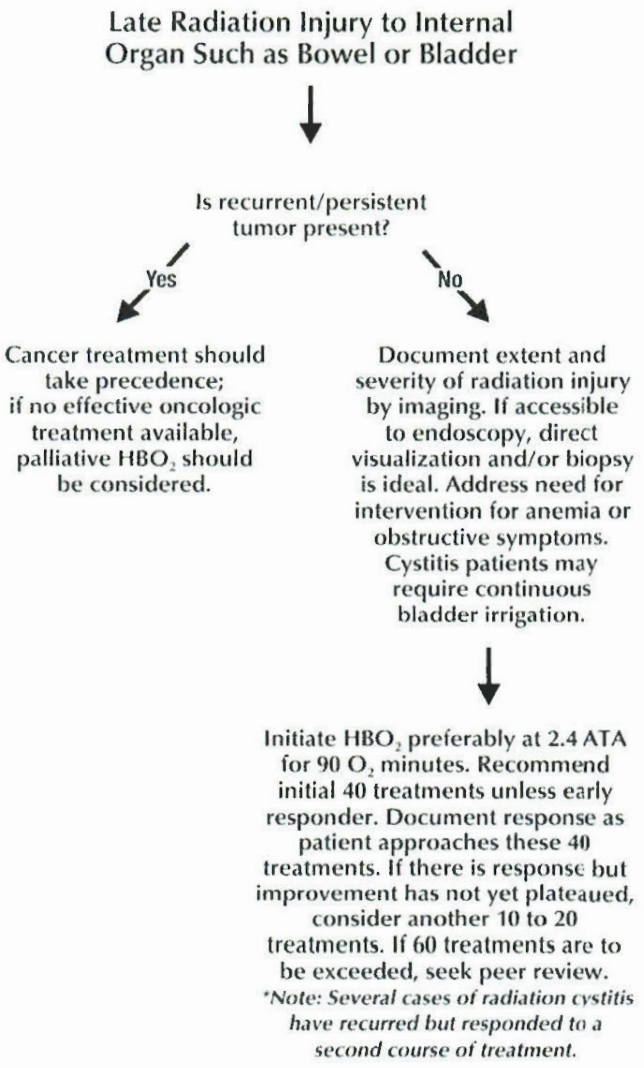


Figure 5.

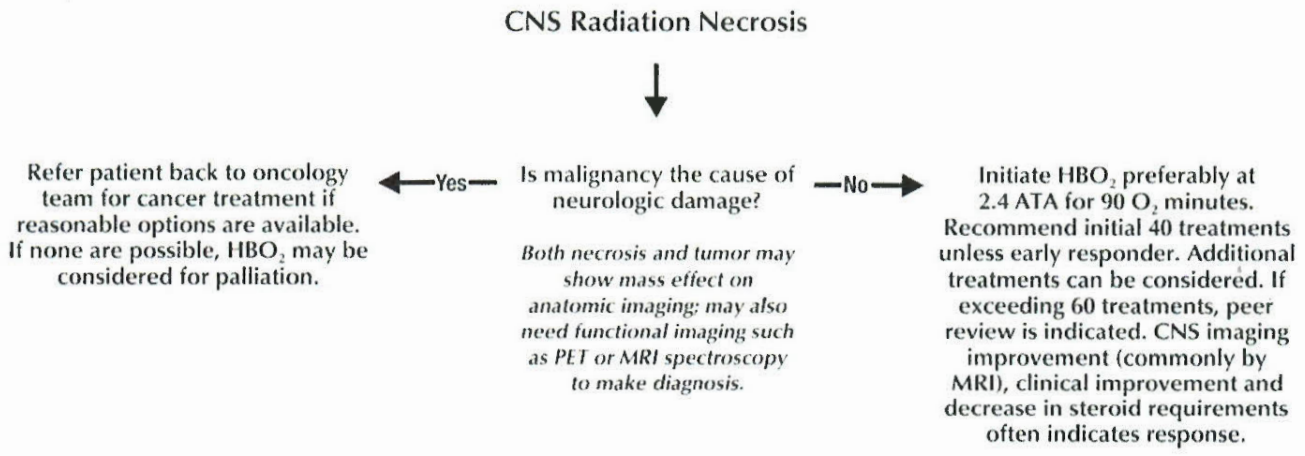
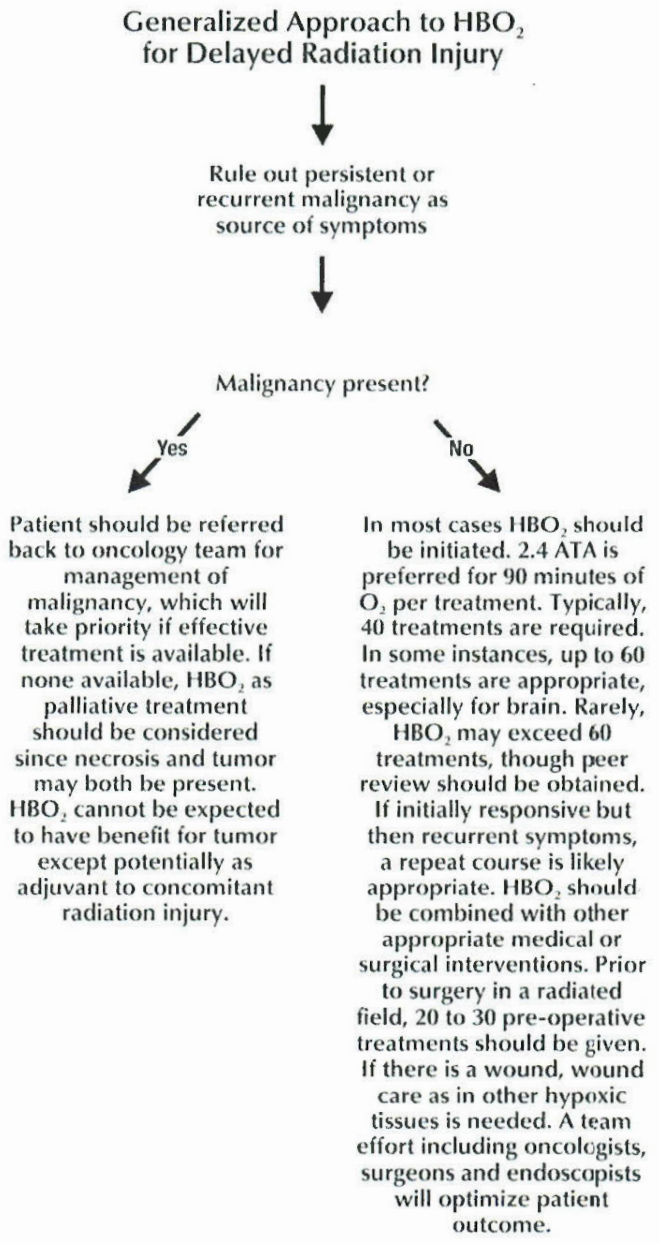


Figure 6.



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