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Delayed Radiation Injury (Soft Tissue and Bony Necrosis)

**Introduction**

Hyperbaric oxygen is among the most studied and frequently reported applications in the treatment of delayed radiation injuries. This application of hyperbaric oxygen to the treatment and prevention of delayed radiation injury will be the topic of this chapter. The management of delayed radiation injury, especially when bone necrosis is present, requires mult-disciplinary management. The nature of delayed radiation injury, the mechanisms whereby hyperbaric oxygen is effective, clinical results, the effects of hyperbaric oxygen on cancer growth and future areas for research will be discussed.

**The Nature Of Radiation Injury**

Radiation injuries should be further sub-classified as acute, sub-acute or delayed complications.(1) Acute injuries are due to direct and near immediate cellular toxicity caused by free radical-mediated damage to cellular DNA. Many cells suffer a mitotic or reproductive death, i.e. enough damage has been rendered to the DNA that successful subsequent mitosis is prevented. Acute injuries are usually self-limited, and are treated symptomatically. However, they can be very debilitating during their duration. Sub-acute injuries are typically identifiable in only a few organ systems, e.g. radiation pneumonitis following the treatment of lung cancer with an onset typically 2 to 3 months after completion of irradiation. Subacute injuries have been shown to occur in the lung with a clinical syndrome mimicking bronchitis. They have also been shown to occur in the spinal cord where temporary demyelinization causes the so-called Lhermitte's syndrome where patient's experience electric-like shocks down their legs with spinal extension. These, too, are generally self-limited but occasionally evolve to become delayed injuries. Some sub-acute injuries may persist for several months. Delayed radiation complications are typically seen after a latent period of six months or more and may develop many years after the radiation exposure. Sometimes, acute injuries are so severe that they never resolve and evolve to become chronic injuries indistinguishable from delayed radiation injuries.(2)These are termed "consequential effects” and are not characterized by a symptom-free latent period. Often, delayed injuries are precipitated by an additional tissue insult such as surgery within the radiation field.

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

**The Etiology Of Delayed Radiation Injury**

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

A more complex model of radiation damage continues to evolve in the radiation oncology community. In the past, radiation oncologists had made a distinction between the causes of acute and delayed injuries. The belief was that they were not directly related. Indeed, it is not uncommon to find a patient with serious acute reactions who will not suffer significant chronic complications or someone with severe chronic complications who had experienced no worse than average acute reactions to the radiation. Radiation scientists now appreciate that the process of radiation injury begins at the time of radiation treatment and involves the elaboration and release of many bioactive substances including very prominently fibrogenetic cytokines.(5)A primary mechanism whereby therapeutic radiation inflicts damage on normal tissues has been termed the fibro-atrophic effect.(4) This model emphasizes the consequences of the observed depletion of parenchymal and stem cells and de-emphasizes the impact of vascular damage. It also highlights the exuberant fibrosis usually found in severely damaged irradiated tissues.(4-6,8) In this model vascular damage and stenosis continue to be recognized as a consistent finding in tissues exhibiting radiation damage including frank necrosis; however, endarteritis as a causative factor for delayed radiation injuries is de-emphasized.

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

Many studies of cytokines and radiation injuries have been accomplished in animal models of radiation-induced pneumonitis.(9) At the present, we are not able to make practical clinical application of these observed associations. No single marker is likely to provide us with a reliable estimate of future radiation damage.(10)Similarly, no practical strategies have as yet been developed to prevent or reduce the production of these cytokines or reduce their impact in a prophylactic fashion. We know that there is a very wide range of tolerance to radiation and that some patients are much more sensitive to radiation injury. If reliable predictors of delayed radiation injury were available, adjustments to the radiation dosing scheme could be made for the radio-sensitive patient. Some patients might be advised to seek alternative therapies instead of radiation. Moreover, prophylactic interventions such as hyperbaric oxygen or other yet to be developed pharmacologic interventions could be applied during the latent period but before the manifestation of the chronic injury. The hope and expectation would be that, by identifying a group at risk and intervening in this group before manifestation of the injury, delayed radiation injury could be prevented or at least reduced in its severity. Obviously this postulate will have to be subjected to clinical trials.

**The Effects Of Hyperbaric Oxygen On Irradiated Tissues**

Because a consistent cause and manifestation of radiation injury is vascular obliteration and stromal fibrosis, the known impact of hyperbaric oxygen in stimulating angiogenesis is an obvious and important mechanism whereby hyperbaric oxygen is effective in radiation injury. HBO2 induces neovascularization in hypoxic tissues. Marx(11) has demonstrated the enhanced vascularity and cellularity in heavily irradiated tissues after hyperbaric oxygen therapy by comparing histologic specimens from patients pre- and post- hyperbaric oxygen. Marx6 has also demonstrated the serial improvement in transcutaneous oxygen measurements of patients receiving hyperbaric oxygen as an indirect measure of vascular improvement. Marx et al(12) in an animal model have shown increased vascular density in rabbit mandibles after exposure to hyperbaric oxygen.

Feldmeier and his colleagues(7,8) in a murine model of radiation damage to the small bowel have shown that prophylactic hyperbaric oxygen 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 and compliance included a mechanical stretch assay as well as quantitative histologic assays of fibrosis in the tunica media of the animal bowel utilizing Mason's trichrome staining.

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

The hyperbaric study group headed up by Dr. Thom(13,14) at the University of Pennsylvania has recently published two studies demonstrating that hyperbaric oxygen can mobilize stem cells by increasing nitric oxygen. This mechanism has not as yet been proven to have a major impact on irradiated tissues. However, a putative effect on increasing stem cells at the site of radiation injury is confirmed to some extent by Marx's(6) demonstration of increased cellularity and vascularity in patients who have received hyperbaric oxygen for mandibular osteoradionecrosis.

The impact of hyperbaric oxygen in terms of its beneficial effects is likely to involve all three of the above mechanisms in irradiated tissues: 1) Hyperbaric oxygen stimulates angiogenesis and secondarily improves tissue oxygenation; 2) Hyperbaric oxygen reduces fibrosis; and 3) Hyperbaric oxygen is likely to mobilize and stimulate an increase of stem cells within irradiated tissues. The third mechanism is at this point putative and remains to be proven in radiation damaged tissues.

Hyperbaric oxygen has been applied as a therapy for delayed radiation injury for more than 30 years. Informal surveys have shown that at most hyperbaric centers in the U.S., nearly one half of patients receiving hyperbaric oxygen are being treated for radiation injury. Hyperbaric oxygen also has a frequent application in the prevention of mandibular osteoradionecrosis when dental extractions are required from heavily irradiated mandibles. The following sections will address the application of hyperbaric oxygen to radiation complications on an anatomic basis beginning with mandibular osteoradionecrosis.

**Hyperbaric Oxygen As Treatment For Mandibular Radiation Necrosis (ORN)**

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

The likelihood of mandibular necrosis as a result of therapeutic radiation varies widely among several reports. Bedwinek(15) has reported a 0% incidence below doses of 6,000 cGy increasing to 1.8% at doses from 6,000 to 7,000 cGy and to 9% at doses greater than 7,000 cGy. In his comprehensive review of radiation tolerance, Emami(16) estimates a 5% incidence when a small portion of the mandible (less than 1/3) is irradiated to 65 Gy or higher and a 5% incidence at 60 Gy or higher when a larger volume of the mandible is irradiated. It has been reported that 85% or more of cases resulting in exposed mandibular bone will resolve spontaneously with conservative management.(17) Unfortunately the remaining cases generally become chronic and may become progressive, often further complicated by associated soft tissue necrosis.

Much of the early work in this area considered radiation induced mandibular necrosis to be a subset of mandibular osteomyelitis.(11) Also, hyperbaric oxygen was delivered frequently as the sole treatment for mandibular necrosis without appropriate surgical management after failure of more conservative therapy. Although many cases would show temporary improvement, almost all cases of moderate to severe ORN would recur if hyperbaric oxygen was administered without appropriate surgical intervention.(18)

Dr. Robert Marx, D.D.S.(18,19)elucidated many basic principles in the etiology and management of mandibular ORN which have led to a rationale approach to its management. He has provided several key principles in the understanding of the pathophysiology of mandibular necrosis. He has demonstrated that infection is not the primary etiology of mandibular necrosis by obtaining deep cultures of affected bone and showing the absence of bacteria. We now understand that osteoradionecrosis is the result of an avascular, aseptic necrosis. Marx(6) has also shown that for hyperbaric oxygen to be consistently successful, it must be combined with surgery in an optimal fashion. Marx has developed a staging system for classifying mandibular necrosis. This staging system is applied to determine the severity of mandibular necrosis. In addition it permits a plan of therapeutic intervention, which is a logical outgrowth of the stage/severity of necrosis.

**Stage I ORN**: This stage includes those patients with exposed bone who have none of the serious manifestations found in Stage III and described below. Generally, before hyperbaric oxygen, these patients have had chronically exposed bone or they have rapidly progressive ORN. These patients begin treatment with 30 HBO2sessions followed by only minor bony debridement. If these patients' response is adequate, an additional 10 daily treatments are given, and the patients are followed to complete clinical resolution.

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

**Stage III ORN**: In addition to those failing treatment in Stage I or II, patients who present initially with grave prognostic signs such as pathologic fracture, orocutaneous fistulae or evidence of lytic involvement extending to the inferior mandibular border are treated 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. 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 and in Stages I and II. Stage III patients receive 30 daily hyperbaric treatments prior to mandibular resection followed by 10 post-resection treatments. Typically after a period of several weeks, the patients complete a reconstruction which may involve various surgical techniques including free flaps or myocutaneous flaps. In its original design, the reconstruction made use of freeze-dried cadaveric bone trays from a split rib or iliac crest combined with autologous corticocancellous bone grafting. In his original work at Wilford Hall USAF Medical Center, Marx had reconstruction patients complete a full additional course of hyperbaric treatments in support of the reconstruction. Marx has subsequently found that the vascular improvements accomplished during the initial 40 hyperbaric exposures are maintained over time and patients can undergo reconstruction without a second full course of HBO2. Patients do receive 10 hyperbaric treatments after the reconstructive surgery to support initial tissue metabolic demands.

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

Feldmeier and Hampson(20) 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 were case series. A single study by Tobey et al(21)was a positive randomized controlled trial. It was a small study with only 12 patients enrolled; however, it was double blinded and reported to be a positive trial by the authors. Details of randomization and outcome determinants were not clearly stated. Patients received either 100% oxygen at 1.2 ATA or 2.0 ATA. The paper states that those treated at 2.0 ATA "experienced significant improvement” compared to the control group.

In this review, only one report of the remaining 13 publications, the publication by Maier et al,(22) failed to report a positive outcome in applying hyperbaric oxygen to the treatment of mandibular ORN. Maier and colleagues added hyperbaric oxygen to their management only after the definitive surgery was done. They failed to heed Marx's guidance that the optimal management of mandibular ORN requires that the majority of HBO2 be given prior to surgical debridement, resection or reconstruction in order to improve the quality of tissues prior to surgical wounding.

Since the review by Feldmeier and Hampson(20) several additional papers have been added to the literature. A multi-institutional randomized controlled trial by Annane et al(23) reported negative results in their study applying hyperbaric oxygen to Marx Stage I ORN. These results have created a stir in the hyperbaric oxygen community, and have prompted criticism of its methods from several sources. Patients were randomized to receive either 90 minutes of 100% O2 at 2.4 ATA or a breathing gas mix equivalent to air at seal 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 2 decades earlier Marx had shown an absolute necessity of surgically eradicating all necrotic bone. The need to debride all necrotic bone to achieve resolution was also confirmed by Feldmeier et al in their review of chest wall necrosis including some cases with ORN of the ribs and sternum.(24)

Additional criticisms of this study by Annane(23) have been made. Moon et al(25) have shown that nearly 2/3's of the hyperbaric group received fewer than 22 hyperbaric treatment. Laden(26) 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. This gas mix was designed to provide an inspired oxygen partial pressure equivalent to air at seal level.

In another recent report, Gal and associates(27) have published their results in treating a series of 30 patients with Marx Stage III mandibular ORN with debridement and reconstruction employing microvascular anastomosis. Twenty-one of these patients had previously been treated with hyperbaric oxygen without resolution, although it is not clear that any of these patients received a full course of treatment. At least some had had some debridement prior to coming to Gal. Once in the author's hands, they all had appropriate debridement and reconstruction with free flaps. Those patients who had not seen hyperbaric oxygen previously had a complication rate of 22% while the group who had received at least some hyperbaric oxygen had a much higher rate of complications 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 refractory mandibular ORN. Obviously, those principles previously established by Marx, i.e. an emphasis on pre-surgical hyperbaric oxygen, debridement of all necrotic bone followed by reconstruction with post-operative hyperbaric oxygen were not followed. The authors of this paper also discuss that Marx Stage III ORN patients represent a heterogeneous group with a broad range of injuries, severity of injuries, and a subsequent broad range of outcomes.

Teng and Futran(28)have recently published their opinion that hyperbaric oxygen has no role in treating ORN. Their article presents no new clinical data and is a review article. The authors base their conclusions on the Annane study and the advancement of the fibro-atrophic model of radiation injury as now being dominant in the opinion of most experts of radiation pathology. Mendenhall,(29) a radiation oncologist from the University of Florida, in an editorial accompanying the Annane paper in the Journal of Clinical Oncology points out that the Annane paper was underpowered and therefore subject to question. He goes on, however, to state his belief that hyperbaric oxygen is not indicated for mandibular ORN although he remarks that it is hard to understand why the HBO2 group in the Annane study did worse than control.

Suffice it to say that these recent papers addressing the efficacy of hyperbaric oxygen in the treatment of ORN have expressed negative opinions. Only one was a randomized controlled trial, and it is subject to the criticisms in design discussed above. If we look at the total body of literature reporting the impact of hyperbaric oxygen on mandibular ORN, we find the following: In the publications reviewed in the Feldmeier/Hampson review,(20) 371 cases of mandibular ORN are reported with a positive outcome in 310 or 83.6%. Unfortunately, some of the papers report improvement rather than resolution as their outcome determinate. Of course a better determination of outcome would be resolution. In Marx's(6) reports, resolution is reported in 100%. Marx also indicates that success in Stage III patients requires not only re-establishment of mandibular continuity but also rehabilitation with a denture for cosmesis and mastication. By contrast if we look at the recent "negative” trials, only 22 patients are included in the Gal report(30) and 31 patients randomized to hyperbaric oxygen in the Annane(26) trial for a total of 53 patients. Practitioners of hyperbaric oxygen who treat mandibular ORN must do so in a multi-disciplinary manner and insure that treatment includes an oral surgeon who can accomplish the needed extirpation of necrotic bone.