11. DELAYED RADIATION INJURIES (SOFT TISSUE AND BONY NECROSIS)

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Rationale

Radiation injuries should be differentiated as acute, sub-acute or delayed complications (1). Acute injuries are due to direct cellular toxicity caused by free radical-mediated damage to cellular DNA and are usually self-limited and 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. These, too, are generally self-limited but occasionally evolve to become delayed injuries. Delayed radiation complications are typically seen after a latent period of six months or more and may develop many years after the radiation exposure. Often, they are precipitated by an additional tissue insult such as surgery within the radiation field. Although the etiology of delayed injuries may vary somewhat among organ systems, the hallmark of delayed radiation injury is endarteritis with tissue hypoxia and secondary fibrosis (2). Recently, it has become apparent that the evolution of radiation injury is a continuum of events rather than several discrete occurrences (3-5). The elaboration of fibrogenic cytokines begins at the time of irradiation. This recognition may permit the development of predictive assays to identify those patients at high risk for radiation injury prior to its manifestation and permit prophylactic intervention prior to its expression. Such intervention might include hyperbaric oxygen therapy.

Hyperbaric oxygen (HBO2) has been utilized effectively for manifest chronic radiation injuries for many years. The site to which it has been applied for the longest period of time and with the most publications supporting its application is the mandible (6-24). The success in treating mandibular osteoradionecrosis has led researchers to apply HBO2 to radiation injuries at other sites involving other organ systems.

Hyperbaric oxygen has been shown to induce neovascularization and increased cellularity in irradiated and other hypoxic tissues. Marx and co-workers have shown in both an animal experimental model and with serial transcutaneous oxygen measurements in clinical subjects that HBO2 does increase vascular density and resultant tissue oxygen content (16,20,25). Feldmeier and colleagues have shown with several assays in an animal model that tissue fibrosis can also be reduced with the application of HBO2 given in a prophylactic mode (26,27). Marx had previously established the principle of prophylactic intervention in the setting of tooth extractions and alveoloplasty from heavily irradiated mandibles (28). Dental extractions or other surgical procedures are fraught with high complication rates when done in heavily irradiated tissues without the benefit of preoperative HBO2 therapy (29-33).

In the sections that follow, the application of HBO2 treatment to injuries of several organ systems will be discussed.

Hyperbaric Oxygen as Treatment or Prophylaxis for Mandibular Radiation Necrosis

The most widely accepted 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. Many 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 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.(34) In his comprehensive review of radiation tolerance, Emami 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 (35). It has been reported that 85% or more of cases resulting in exposed mandibular bone will resolve spontaneously with conservative management (36). 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. Also hyperbaric oxygen was delivered essentially as the sole treatment for mandibular necrosis without appropriate surgical management after failure of more conservative therapy.

Robert Marx, D.D.S. has provided several key principles in the understanding of the pathophysiology of mandibular necrosis and its management. (37) 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 avascular aseptic necrosis. Marx has also shown that for hyperbaric oxygen to be consistently successful, it must be combined with surgery in the optimal fashion. (14) Marx has developed a staging system for classifying mandibular necrosis. (14,16) 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 of necrosis.

Stage I ORN (osteoradionecrosis) includes those patients with exposed bone who have none of the serious manifestations of those in Stage III. Generally these patients have had chronically exposed bone or they have rapidly progressive ORN. These patients begin treatment with 30 HBO2 sessions with either no debridement or only minor bony debridement planned. If these patients progress satisfactorily an additional 10 treatments are given. If patients are not progressing appropriately or if a more major debridement is needed, they are advanced to Stage II and they receive the necessary surgical debridement at 30 treatments followed by 10 postoperative treatments. Surgery for Stage II patients must maintain mandibular continuity. If mandibular resection is required, patients are advanced to Stage III. Patients who present with grave prognostic signs such as pathologic fracture, orocutaneous fistulae or evidence of lytic involvement extending to the inferior mandibular border are treated as in Stage III from the outset. Patients from Stage I or II can also be advanced to this stage if they do not make appropriate progress. In Stage III patients are entered into a reconstructive protocol where a mandibular resection is followed by a planned reconstruction. Marx has established the principle that all necrotic bone must be surgically eradicated. Stage III patients receive 30 hyperbaric treatments prior to their 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. He has now shown that the vascular improvements accomplished during the initial 40 hyperbaric exposures are maintained over time

and patients can undergo reconstruction without the second full course of HBO2. Patients do receive 10 hyperbaric treatments after the reconstructive surgery to support tissue metabolic demands.

Marx 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. (20) Unfortunately the majority of patients (68%) required treatment in Stage III 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, cosmetics and re-establishment of dentition for mastication, are necessary components in improving quality of life in this group of patients.

Extraction of teeth from heavily irradiated jaws is a common precipitating factor for mandibular necrosis. Marx 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 HBO2 versus penicillin prophylaxis. (28) Those patients assigned to the hyperbaric group completed 20 pre-extraction HBCO2 treatments with ten additional post-extraction hyperbaric treatments. Thirty-seven patients were treated in each group. In the penicillin group, some 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 requiring treatment as Stage III patients while neither patient with ORN from the hyperbaric group required a discontinuity resection and both resolved as Stage I ORN patients with additional hyperbaric oxygen.

The important principles (advocated by Marx) in the treatment and prevention of ORN include an emphasis on pre-surgical hyperbaric oxygen to allow better tolerance to surgical wounding. The need to eradicate all necrotic bone surgically is also emphasized. In the tissue deficient patient the use of myocutaneous flaps are routinely employed.

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. A review article by Feldmeier discusses the published literature related to hyperbaric oxygen for these indications (38). A total of 19 papers are discussed (6-24). All but one of these shows a positive benefit for HBO2. In the single negative publication, the authors fail to heed Marx's advice and do not make use of pre-operative hyperbaric oxygen.

Laryngeal Necrosis and Soft Tissue Necrosis 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% (39,40). However, when persistent edema, fetid breath or visible necrosis persist for more than 6 months after completion of irradiation, traditional recommendations have been to accomplish a laryngectomy because the likelihood of persistent tumor is very high. Also, previous treatment of pure laryngeal cartilaginous necrosis has not been successful (41,42). Chandler has established a system to grade the severity of laryngeal necrosis (43). Patients suffering from Grade 3 or 4 necrosis have a high likelihood of requiring laryngectomy. In fact most texts in Head and Neck Oncology recommend laryngectomy if severe symptoms of necrosis persist for more than 6 months.

Three institutions have published their experience in applying hyperbaric oxygen to the treatment of radiation laryngeal necrosis (44-46). In these papers the outcome in a total of 35

cases is reported and only 6 patients were failures to treatment and required laryngectomy. The other 29 patients maintained their voice box and most had good voice quality.

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. Most of these deal with soft tissue necrosis of the neck and failing flaps within irradiated fields. In the textbook Hyperbaric Medicine Practice edited by Dr. Kindwall, Marx has reported extensive experience in treating soft tissue radiation injuries of the head and neck (47). In a controlled but non-randomized report of 160 patients, he has compared wound infection, dehiscence and delayed healing in the hyperbaric group versus a control group. He found that HBO2 patients experienced 6% wound infection versus 24% control; 11% dehiscence versus 48% control; and 11% delayed wound healing versus 55% control. All differences are statistically significant when the Chi square test is applied.

Other authors have also duplicated these results. Davis and his colleagues have reported successful treatment in 15 of 16 patients with soft tissue necrosis of the head and neck including many with extensive necrotic wounds (48). In 1997 Neovius and colleagues reported a series of 15 patients treated with hyperbaric oxygen for wound complications after surgery within an irradiated field (49). They compared this group to a historical control group from the same institution. Twelve of the 15 patients in the hyperbaric group healed completely with improvement in 2 and only 1 without benefit. In the control group only 7 of 15 patients healed. Two patients in the control group also developed life-threatening hemorrhage and 1 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 that exsanguinated as the result of a soft tissue necrosis of the neck which progressed to erode into the carotid artery or other major vessel.

In another group of patients, Feldmeier and colleagues have reported the successful prophylactic treatment of patients undergoing radical surgical resection for salvage cure of head and neck cancers after failing initial treatment including full course irradiation (50). Serious surgical complications, including occasional fatalities, have been reported to occur-in over 60% of such patients without the benefit of HBO2 (51-53). With a short course of HBO2 (median number of treatments 12), 87.5% of patients healed with no serious complications and no deaths occurred in the immediate postoperative period.

Chest Wall Necrosis

Radiation therapy after lumpectomy has become the preferred treatment for most early breast cancers. After this treatment, fat necrosis of the intact breast has been reported but is a fairly uncommon clinical problem. Hyperbaric oxygen has not been reported as a therapeutic strategy in this condition. Radiation therapy is frequently used as an adjuvant treatment following mastectomy in more advanced cancers for large tumors or when axillary metastases are present. When a patient is irradiated after mastectomy, the radiation dose to the skin is intentionally high with the goal of preventing tumor failure in the skin. As a result of this standard radiation technique, most women irradiated after mastectomy are subject to significant acute radiation reactions. Frank necrosis of the chest wall is fairly uncommon but is very difficult to manage when it does occur. Traditional treatment for chest wall necrosis has required extensive surgical debridement and frequently closure with omental or myocutaneous flaps originating outside the radiation field to insure vascular supply, which is unimpaired by radiation vascular injury.

Hart and Mainous in 1976 reported the successful application of hyperbaric oxygen as an adjunct to skin grafting in women treated for necrosis of the chest wall after mastectomy (7). Feldmeier and colleagues in 1995 reported the outcome in applying hyperbaric oxygen as treatment of both soft tissue and bony necrosis of the chest wall (54). All cancer-free patients who suffered only soft tissue necrosis were treated successfully. However, only 8 of 15 patients treated for bony necrosis resolved. It appears that these patients failed at least in part because of inadequate debridement of residual necrotic bone. Marx had previously demonstrated the necessity of total extirpation of necrotic bone for the treatment of mandibular osteonecrosis (12-14). This general principle should apply to osteoradiaonecrosis at any site.

Carl and his associates in 2001 reported the outcome of 44 patients who suffered complications following lumpectomy and irradiation for early breast cancers (55). 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 various degrees of severity. The severity of symptoms was assessed with a score for each patient based on a modified SOMA-LENT score. Only patients with at least grade 3 pain (persistent and intense) or a summed SOMA-LENT score of 8 were studied. 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. Thirty-two patients agreed to undergo hyperbaric oxygen treatment while 12 women refused HBO2 and constituted the control group. Hyperbaric oxygen treatments resulted in a statistically significant reduction in the post treatment SOMA-LENT scores in women receiving treatment compared to those who did not. Fibrosis and telangectasia were not reduced. Women in the control group continued to demonstrate symptoms at the completion of the trial with no improvement in pain or edema. Seven women in the hyperbaric group had complete resolution of their symptoms at the end of the trial.

Radiation Cystitis

Since 1985, a number of authors have published reports of radiation cystitis treated with hyperbaric oxygen. A recent review discovered 14 such publications (56-69).All but one of these reported a positive outcome with resolution in the vast majority of patients. The largest series was published by Severs and colleagues and was a prospective but non-randomized trial. A total of 40 patients were treated in this report with resolution in 36 (64). If we combine all of these reports, we find 136 patients treated with hyperbaric oxygen and resolution in 112 patients or 82.4%.

Many of the patients included in the above-cited reports had already failed conservative management including intravesical treatment with alum or formalin. Severe hemorrhagic cystitis is a life threatening disorder. Many patients require urinary diversions or cystectomy. Cheng and Foo have reported the results in treating 9 patients with severe radiation induced hemorrhagic cystitis (70). Forty-four percent of these patients died as a result of their radiation induced hemorrhagic cystitis in spite of aggressive surgical intervention.

Radiation Proctitis and Enteritis

A controlled animal study has been reported by Feldmeier and associates wherein HBO2 was shown to be highly successful in preventing radiation-induced enteritis when experimental animals received HBO2 in a prophylactic setting 7 weeks after radiation exposure (26,27). When animals were euthanized 7 months after the radiation exposure, both gross and histologic morphometry demonstrated a statistically significant reduction in signs of enteritis in the

experimental group compared to the radiation only control group. Both quantitative histologic morphometry and a mechanical stretch test demonstrated reduction in submucosal fibrosis and an increase in mechanical compliance for hyperbaric treated animals.

Nine clinical papers reporting the results of hyperbaric oxygen in the treatment of enteritis or proctitis have been identified in a recent review by Feldmeier (71-79). These publications present some 105 cases. Thirty-four (32%) of these patients were treated with complete resolution while another 67 (64%) had improved symptoms. Four percent of patients had no benefit from treatment.

Bredfeldt and Hampson have reported in abstract form their experience in applying hyperbaric oxygen to the treatment of 19 patients with chronic radiation enteritis (80). Injuries included radiation proctitis (some with ulceration), gastroduodenal bleeding, and an esophageal ulcer. Patients were treated with 30 hyperbaric treatments at 2.36 atm abs. Complete resolution was achieved in 47%, with improvement in another 37%, and no improvement in the remaining 16%. A case report by Neurath and colleagues documents the successful resolution of severe malabsorption due to established radiation enteritis in a 53 year old female following 20 hyperbaric treatments at 3.0 atm abs for 90 minutes (81).

Other Abdominal and Pelvic Injuries

In 1978 Farmer and associates reported a single case of vaginal necrosis which resolved with hyperbaric oxygen (9). In 1992, Williams and colleagues reported their results in treating 14 patients with vaginal necrosis (79). Thirteen of 14 patients had complete resolution although one patient required a second course of hyperbaric oxygen. In 1996 Feldmeier and his co-authors published their results in a review of 44 patients treated with HBO2 for a variety of pelvic and abdominal injuries (71). The results in treating large and small bowel injuries were included in the discussion in the section above. Thirty-one patients received at least 20 hyperbaric treatments for radiation injuries to the perineum, groin, vagina and pelvic bone. Twenty-six of these patients had complete resolution of their radiation injury.

If we add those patients reported by Farmer, Williams and Feldmeier, we find that 40 of 46 patients (87%) had complete resolution of their necrosis with hyperbaric treatment. Only a single patient in the three papers who suffered from soft tissue injury only failed to achieve complete resolution.

Radiation Injuries of the Extremities

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

In the recent review by Feldmeier and Hampson only 2 studies were discovered which report the results of hyperbaric treatment in radiation injuries of the extremities (38). Farmer and associates in 1978 reported a single patient treated for radiation necrosis of the foot without improvement (9). Feldmeier et al in 2000 reported a series of 17 patients treated for extremity radiation necrosis (82). Eleven of 17 patients had complete resolution. In those patients in whom follow-up is available and who were not found to have recurrent malignancy in the wound, eleven of 13 or 85% resolved.

Certainly, the published experience in applying hyperbaric oxygen to radionecrosis of the extremities is limited. However, based on the successful treatment of radiation necrosis of both bone and soft tissues in other anatomic sites, it is reasonable to recommend hyperbaric oxygen for this indication. Oxygen in the hyperbaric setting has often been referred to as a "drug." Just as an antibiotic can be recommended for treatment of an infection of one anatomic site based on success at other sites, we can recommend hyperbaric oxygen for radiation injury of the extremities based on success in other tissues.

Neurologic Injuries Secondary to Radiation

In the review article previously cited, Feldmeier and Hampson have identified 12 publications that report hyperbaric oxygen treatment for a variety of neurologic injuries(38).These include radiation induced transverse myelitis (spinal cord injury), brain necrosis, optic nerve injury and brachial plexopathy.

In 1976, Hart and Mainous reported the treatment of 5 cases of transverse myelitis (7) and Glassburn and Brady reported 9 cases of transverse myelitis in 1977 (83). In the report by Hart, there was no improvement in motor function while in Glassburn's report 6 of 9 patients had improvement including some restoration of motor function. In 2000 Calabro and Jinkins reported a single case of transverse myelitis treated with hyperbaric oxygen who showed both clinical and MRI imaging evidence of improvement (84). In an animal study by Feldmeier et al, delay but no permanent prevention of myelitis was seen for HBO2 given before detectable signs of myelitis seven weeks after a fairly extreme radiation exposure (85). There are no other known successful treatments for radiation induced myelitis, and besides the obvious drastic impact on quality of life with resultant paralysis, there is a high incidence of mortality as a result of this condition. Two thirds of patients die within 4 years of onset. Although the outcome for hyperbaric treatment has not been reproducibly successful, given the dire consequences of fully manifest transverse myelitis and the total absence of other effective treatments, hyperbaric therapy should be considered based on humanitarian concerns.

Several publications report the use of hyperbaric oxygen for radiation induced brain necrosis. In their 1976 paper Hart and Mainous report a single case of radiation caused brain injury, which improved with HBO2 (7). Chuba and colleagues have reported a series of 10 pediatric patients with radiation-induced brain necrosis who were treated with hyperbaric oxygen (86). All children improved initially. At the time of their publication, four patients had died due to recurrent tumor and 5 of the 6 remaining patients had maintained their neurologic improvement as a result of hyperbaric treatment. Leber and colleagues have reported 2 cases of patients who developed brain necrosis after radiosurgery procedures for arteriovenous malformations. Both of these patients had reduction in the size of necrosis after hyperbaric oxygen therapy as indicated by imaging studies and 1 had complete resolution (87). Cirafsi and Verderamae have published their results in a single case of brain necrosis secondary to radiation (88). This patient had no improvement with hyperbaric oxygen. The patient had also failed to respond to steroids and anti-coagulants. If we combine the results from the above cited papers, we find that 8 of 14 patients demonstrate improvement for brain necrosis. No other treatment short of craniotomy and resection of the necrotic focus has been successful, and intervention with hyperbaric oxygen should be considered.

Gesell and associates have reported the most extensive experience to date in applying hyperbaric oxygen to the treatment of radiation-induced brain necrosis (89). At the 2002 Annual Meeting of the Undersea and Hyperbaric Medical Society, Dr. Gesell reported the results in

treating 29 patients with radiation induced brain necrosis. Seventeen of 29 patients had improved neurologic examinations, and 20 of 29 were able to decrease their steroid requirements. At the same meeting Dear and colleagues from Duke presented their experience in treating 20 patients with radiation-induced brain necrosis (90). Eleven patients had received radiation as part of their management for Glioblastoma Multiforme, an extremely lethal brain malignancy. Seven of these 11 patients were dead of tumor within a short time following hyperbaric oxygen and obviously had active tumor at the time of treatment. It is very likely that the tumor itself contributed to the neurologic deficits manifested by the patients. In the other 9 patients, who were treated for other tumors, eight were subjectively improved and 3 had demonstrable improvement. When we combine the results from these 6 publications, we find that 29 of 63 (46%) patients reported had a positive therapeutic outcome with hyperbaric oxygen. No other treatments short of surgical resection of the necrotic focus have been effective to date.

Four publications discuss hyperbaric oxygen as treatment for radiation induced optic neuritis (91-94). A total of 19 patients are included in these reports and only 4 of the 19 are reported to have experienced improvement. Borruat et al have reported on a single patient with bilateral optic neuritis (93). 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 HBO2. The support for hyperbaric oxygen in this condition is only anecdotal at best. However, if consideration is given to the dire consequences with resulting blindness and the lack of other effective treatment, a trial of hyperbaric therapy with prompt intervention is recommended.

A randomized controlled trial by Pritchard and associates has been conducted in regard to hyperbaric oxygen therapy for brachial plexopathy (95). Unfortunately, this trial is negative in terms of failing to show a statistically significant improvement in the hyperbaric group compared to the control group. The median time of entry into the study after development of the neuropathy was 11 years and the injuries were certainly fixed in over time. Though no improvement was observed, the hyperbaric group of patients had less further deterioration than did the control group over after treatment. 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.

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

Special Consideration:

Hyperbaric Oxygen as A Prophylaxis for Radiation Injury: Most of the literature cited above reports the results from application of HBO2 to already expressed radiation injury. A growing body of literature supports the use of HBO2 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 HBO2 is that by Marx where hyperbaric oxygen has been shown to decrease the incidence of mandibular osteoradionecrosis from 29.9% to 5.4% when a course of 20 HBO2 treatments was delivered prior to dental extractions from heavily irradiated mandibles (28). In this protocol an additional 10 treatments are delivered after extractions to support tissue metabolic demands post surgical wounding.

Marx has also reported the benefit of hyperbaric oxygen in the enhancement of osseointegration of dental implants in irradiated bone (33). Most oral surgeons will not attempt dental implants in irradiated jaws due to the very high rate of failure and the risk of precipitating osteoradionecrosis. Both Marx and Grandstrom 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 (96,97). Using the same protocol as for osteoradionecrosis prophylaxis (20 preoperative and 10 postoperative HBO2 treatments), Marx has achieved an 81% osseointegration success rate with prevention of osteoradionecrosis in 100% of the patients so treated. Nineteen percent failed to osseointegrate as compared to 6% in non-irradiated patients undergoing dental implants. Ueda and colleagues have reported a success rate of 92.3% (in a total of 21 implants) using a similar regimen of HBO2 in conjunction with dental implants (98).

As already cited above, Feldmeier et al 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 (50). 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 HBO2. Pomeroy and his associates have reported their results in applying preoperative hyperbaric oxygen as an adjunct to surgery for soft tissue injuries of the pelvis (99). All 5 patients in this report had an uneventful postoperative course, although 2 of 5 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 even when there is no surgical trauma (26).

A promising area for clinical application will be the further definition of prophylactic hyperbaric oxygen in the prevention of radiation injury. The development of reliable biochemical predictors of radiation injury would permit the identification of the population at risk for development of radiation injury. At the present time, a reasonable approach is to provide adjunctive HBO2 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 HBO2 (20,52,53,99,100). Third party insurance carriers must be convinced that such prophylactic intervention is not only valuable for humanistic reasons but also for financial reasons. It is hoped that literature cited above will provide the individual practitioner with the needed documentation to make a case for the prophylactic application of HBO2. Hyperbaric oxygen in a preventative setting is likely to be more cost effective than a prolonged course of rehabilitation and reconstructive surgeries in a corrective fashion. In summary the use of hyperbaric oxygen prior to surgery in an irradiated field may prevent or decrease the incidence of catastrophic events such as wound breakdown with bony or hardware exposure, vascular rupture, infection, fistula formation, and/or flap loss and prevent further surgical intervention in an already compromised patient.

Concerns Related to Potential Carcinogenesis or Cancer Growth Enhancement

A frequently expressed concern by those considering hyperbaric oxygen for a patient with radiation injury is the fear that hyperbaric oxygen will somehow accelerate malignant growth or cause a dorminant malignancy to be re-activated. In Marx's very large group of patients treated with HBO2 for radiation injury of the mandible, there was no increased likelihood of tumor

recurrence or second tumor development (20). In 1994, Feldmeier and his colleagues reviewed the available literature related to this issue. An overwhelming majority of both clinical reports and animal studies reviewed in this paper showed no enhancement of cancer growth. A small number of reports actually showed a decrease in growth or rates of metastases (101). Feldmeier updated this material for the Consensus Conference held in 2001 jointly sponsored by the European Society of Therapeutic Radiology and Oncology (ESTRO) and the European Committee for Hyperbaric Medicine (ECHM) (102). In this update, Feldmeier emphasized the differences known in tumor and wound healing angiogenesis with similar but distinct processes operative in each case. He also showed that there are significant differences in the growth and inhibition factors, which modulate angiogenesis, in both circumstances. He summarized the literature demonstrating that tumors which are hypoxic are less responsive to treatment, less subject to death by apoptosis and more prone to aggressive growth and lethal metastases. Most experienced practioners of hyperbaric oxygen no longer fear that hyperbaric oxygen will promote malignant growth. An even more recent review has been accepted for publication in Undersea and Hyperbaric Medicine (103).

Utilization Review

Utilization review should be accomplished after 60 treatments when HBO2 is applied to the treatment of radiation injury. Characteristically, most treatment courses for radiation injury will be in the range of 35 to 45 treatments when the course of treatment is carried out with daily treatments at 2.0 to 2.5 atm abs (ATA) for 90 to 120 minutes of 100% oxygen.

Cost Impact

Soft tissue and bony radiation necrosis are fortunately uncommon sequelae of therapeutic irradiation. Approximately 600,000 patients receive therapeutic radiation annually in the U.S. The likelihood of serious complications is somewhere between 1 to 5% of the total or potentially between 6,000 to 30,000 patients annually. Frequently, these complications require surgery within an irradiated field where the likelihood of significant postoperative complications is on the order of 50%. By avoiding surgery or supporting surgical healing, HBO2 therapy can significantly reduce the dollar and human costs of radiation complications. Marx has accomplished a dollar cost estimate of the treatment of mandibular osteoradionecrosis (33). In 1992 U.S. dollars, the cost of management is reduced from about $140,000 when HBO2 is not utilized to about $42,000 when HBO2 and surgery are combined in optimal fashion. Similar cost advantages are anticipated in the treatment of radiation injuries of other tissues.

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