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HBO Therapy in the Management of Radionecrosis

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HBO has been used with good results in the management of radionecrosis. This chapter reports on the applications after discussing important background topics, following this outline:

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Introduction

Radiation therapy has proven to be effective in the treatment of malignancies. The goal is to irradiate tumors with minimal adverse effects on the surrounding normal tissue. This is difficult to achieve, and in practice there is usually some degree of residual damage to the tissues after radiotherapy. Theoretically it is possible to destroy all malignancies if the dosage of radiation is raised to high levels. With the limitations of the human body's tissue tolerance to radiation, optimal dosage schedules are followed that provide an acceptable benefit/damage ratio for the patient. Radiation-induced tissue necrosis is a complication even when accepted dosage schedules are followed. A basic knowledge of radiation physics and radiation biology is essential for understanding the pathology of radio-necrosis.

Radiation Physics

There are two types of ionizing radiations with significant biological effects.

- Electromagnetic radiation: a combination of electric and magnetic fields, consisting of bundles of energy called photons. This form of radiation is termed gamma rays if it originates from the atomic nucleus, and x-rays if it originates from the shell around the nucleus.
- Particulate radiation. Examples of this are the heavy radiation particles such as protons and neutrons.

Unit of Radiation

A rad is the amount of radiation of any type that results in deposition of 100 ergs of energy/g of tissue. Directly ionizing radiation transfers energy to the tissue by direct disruption of the atomic structure of the tissue. Indirectly ionizing radiations such as neutrons transfer energy by being absorbed by the tissue atom nuclei, which, in turn, give off directly ionizing charged particles as well as gamma rays and x-rays.

X-rays scatter in tissues whereas heavy radiation particles like proton beams can be focused on targets at depths with peak effect. The tissues in the path of the beam receive minimal radiation.

Radiation Biology

In the initial stages of radiation tissue interaction there are several metastable states and energy transfer processes that

precede chemical changes in the tissues. The indirect effects of radiation are due to reactive species (free radicals derived from water molecules). The chemical changes resulting from radiation are:

- Damage to the protein structure
- Lipid peroxidation
- DNA damage

The cell DNA is a critical target. There is breakage of hydrogen bonds between the strands of DNA and formation of cross links with other DNA molecules and chromosomal proteins. There is some correlation between DNA molecules and chromosomal proteins, and between DNA damage and cellular radiosensitivity. The radiosensitivity of a cell depends upon the stage of the cell cycle at the time of radiation and is greatest just prior to mitosis. The radiosensitivity of the cells is directly proportional to their mitotic activity and inversely proportional to their level of specialization.

The effect of ionizing radiation on the tissues is the sum of the damage to cells in the tissues; damage to the critical cell components of a certain tissue can cause death of the whole tissue or even the whole organ.

Connective tissue (including vascular epithelium) has a radiosensitivity that is intermediate between differentiating intermitotic cells and reverting postmitotic cells. Damage to vascular epithelium with obliteration of the vessels may be responsible for the delayed necrosis following radiation.

Radiation Pathology

Clinicopathological Correlations

The clinicopathological correlation of the sequence of events following radiation is divided into four periods:

- Acute period. First 6 months. During this period there is accumulation of acute organ damage, which may be clinically silent.
- Subacute period. Second 6 months. This is the end of the recovery from the acute period. Persistence and progression of permanent tissue damage is evident during this period.
- Chronic period. Second to fifth year. There is further progression of chronic progressive residual damage. There is deterioration of microvasculature with resulting hypoperfusion, parenchymal damage, and reduced resistance to infections.
- Late clinical period. After the fifth postirradiation year. Further progression of changes in the chronic period with additional effects of aging (premature), and radiation carcinogenesis may manifest during this period.

Whole body irradiation may cause acute radiation sickness, but the localized radiation-induced damage that manifests during the subacute and the chronic periods is relevant to our discussion in this chapter.

Radiation damage progresses slowly and continues long after the radiotherapy has been discontinued. Damaged cells do not reproduce and otherwise normal cells may fail to reproduce because of loss of vascularity. There is loss of collagen and increased fibrosis in the radiated tissues due to low oxygen gradient. Oxygen tension at the center of an uncomplicated radiated area is 5–10 mmHg (Marx & Johnson 1988).

Effect of Radiation on Blood Vessels

Radiation has been shown to produce swelling, degeneration, and necrosis of the endothelium with resulting thickening of the vessel wall. These vascular changes progress slowly after radiation and have been referred to as proliferative endarteritis and necrotizing vasculitis. The arterioles and the capillaries suffer the most damage, whereas the larger vessels are spared.

Effect on Soft Tissues

Skin is the tissue that has been most extensively studied for the effects of radiation in the acute, subacute, and chronic periods. Skin atrophy occurs in the chronic stages and the skin is prone to ulceration with minor trauma. Skin incisions made through previously irradiated areas heal poorly. The underlying soft tissues undergo necrosis due to microvascular occlusion. Radiation may directly affect the mucosal cells of the gastrointestinal and genitourinary tracts producing gastroenteritis and cystitis respectively. A case of laryngeal radionecrosis was treated successfully with HBO (Hsu *et al* 2005).

Radiation Effects on the Nervous System

The effects of radiation on the nervous system are reviewed elsewhere (New 2001). The normal neurons are fairly resistant to the usual doses of radiation. Radiation necrosis is thought to result from complex dynamic interactions between parenchymal and vascular endothelial cells within the CNS.

Radiation Effects on Bone

Bone is 1.8 times as dense as soft tissues and absorbs a larger portion of the incident radiation than do soft tissues.

Radiation affects both the vascular and the cellular components of bone. High doses of radiation damage the blood vessels passing between the periosteum and the surface of the bone, leading to bone death. Radiation upsets the balance between the constantly occurring osteoclastic destruction and osteoblastic construction of adult bone. This leads to osteoporosis and finally osteonecrosis, which usually takes place 4 months to several years following radiation. The usual sites of necrosis are:

- The mandible, generally following radiotherapy of soft tissue tumors of the head and the neck. The mandible absorbs more radiation than the maxilla because of its greater density and shows more necrosis due to its lesser vascularity.
- The ribs, clavicle, and the sternum, usually following radiotherapy of breast cancer.
- The skull, usually following radiotherapy of brain tumors and soft tissue tumors of the scalp.
- Vertebral column, usually following radiation of spinal cord tumors.
- Pelvis and femoral head following radiation of pelvic tumors.

HBO Therapy for Radionecrosis

Rationale

There is no satisfactory treatment of radiation necrosis using the available conventional methods. It is difficult to provide adequate nutrients and oxygen to the devascularized tissues. Radiation ulcers are painful and use of narcotic analgesics can lead to addiction. Reconstructive surgery in the radiated areas has a high failure rate due to healing problems. Frustration with the use of conventional methods has led to the trial use of HBO in the management of radiation necrosis.

HBO raises the tissue pO_2 to within the normal range and stimulates collagen formation at wound edges. This, in turn, enhances the formation of new microvasculature. This provides reepithelialization of small ulcers and provides a better nutritive bed to support grafts and pedicle flaps. Tissue oxygen studies have shown that angiogenesis becomes measurable after 8 treatments with HBO, reaches a plateau at 80%–85% of non-radiated tissue vascularization after 20 treatments, and remains at this level whether or not HBO is continued (Marx *et al* 1985).

The rationale of the use of HBO for nonhealing wounds also applies to radiation necrosis. Osseous implants are sometimes required for reconstruction of bone in radionecrosis. Larsen *et al* (1993) have exposed rabbit tibias to tumoricidal doses of radiation. Adjuvant HBO therapy was shown to improve the amount of histologic integration of

the implants in this compromised situation as compared with contralateral control implants.

HBO is not used in the early postradiation period as it may potentiate the effects of radiation. HBO may have no effect as a prophylactic for radionecrosis because a certain amount of vascular damage should be evident before HBO effect can be observed. In some situations HBO, by resolution of the swelling of the involved tissues, permits a better definition of the tumor tissue, which can be resected surgically. The presence of residual tumor in an ulcer bed, on the other hand, would lead to failure of a skin graft, even if HBO is used.

The benefit of treating radiation injuries with HBO was first reported in 1973 (Mainous *et al* 1973; Greenwood & Gilchrist 1973). Hart & Strauss (1986) reported their treatment of 378 patients with this diagnosis. After deaths and drop-outs for various reasons, 336 patients completed the treatment course of HBO. The reasons for discontinuance of the therapy (contraindications) were recurrence of the tumor, viral infections, and smoking by patients. HBO was considered as an adjunct to surgery and other appropriate medical regimens. Each patient was treated at 2 ATA for 2 h daily in the case of outpatients, or 1.5 h twice daily in the case of inpatients for a total of 120 h or less. If healing is not adequate, the treatment is repeated after a rest period of 3–6 months. As HBO immediately following radiation may have deleterious effects, the authors do not start HBO therapy until 2 months after the last radiotherapy treatment. They concluded that HBO combined with other appropriate treatments reduces the morbidity of radiation injury.

After a review of the literature and his own experience, Davis (1981) concluded:

The clear physiological basis, supported by experimental data, upon which hyperbaric oxygen is useful in radiation necrosis, confirmed by almost identical beneficial results in multiple centers, makes the use of adjunctive hyperbaric oxygen in both soft tissues and osteoradionecrosis compelling indications.

This conclusion still holds good. Review of a cumulative 14-year experience with 124 patients has shown that HBO therapy led to significant improvement in 94% of the cases (Slade & Cianci 1998). The average number of treatments for these patients was 33.1 and the average HBO treatment costs were \$15,800. The patient material covered a wide range of soft tissues affected by radiation necrosis and the treatment protocol was HBO at 2 ATA for 90–120 min daily and occasionally twice daily. The authors feel that a minimum of 30 treatments are necessary and there is need to develop more definite outcome predictors and treatment protocols for soft tissue radiation damage indicators.

The role of HBO in radiation necrosis in the adults is well established now. In order to evaluate this approach in the pediatric population, Ashamalla *et al* (1996) reviewed

the experience at the University of Pennsylvania, Philadelphia. Between 1989 and 1994, ten patients who underwent radiation therapy for cancer as children were referred for HBO therapy. Six patients underwent HBO therapy as a prophylactic measure prior to maxillofacial procedures; dental extractions and/or root canals (four patients), bilateral coronoidectomies for mandibular ankylosis (one patient), and wound dehiscence (one patient). Therapeutic HBO was administered to four other patients; one patient for vasculitis resulting in acute seventh cranial nerve palsy and the other three after sequestrectomy for osteoradionecrosis (mastoid bone, temporal bone, and sacrum, respectively). Osteoradionecrosis was diagnosed both radiologically and histologically after exclusion of tumor recurrence. The number of treatments ranged between 9–40 (median, 30). Treatments were given once daily at 2 ATA for 2 hours each. Adjunctive therapy in the form of debridement, antibiotics, and placement of tympanotomy tubes was administered to two patients. Ages at HBO treatment ranged from 3.5 to 26 years (median, 14 years). The most commonly irradiated site was the head and neck region. The interval between the end of radiation therapy and HBO treatment ranged between 2 months and 11 years (median, 15 years). The median follow-up interval after HBO therapy was 2.5 years (range, 2 months–4 years). Except for two patients who had initial anxiety, nausea, and vomiting, HBO treatments were well tolerated. In all but one patient, the outcome was excellent. In the six patients who had prophylactic HBO, all continued to demonstrate complete healing of their orthodontal scars at last follow-up. In the four patients who received HBO as a therapeutic modality, all 4 had documented disappearance of signs and symptoms of radionecrosis and two patients demonstrated new bone growth on follow-up CT scan. One patient with vasculitis and seventh cranial nerve palsy had transient improvement of hearing; however, subsequent audiograms returned to baseline. It was concluded that the use of HBO for children with radiation-induced bone and soft tissue complications is safe and results in few significant adverse effects. It is a potentially valuable tool both in the prevention and treatment of radiation-related complications.

Management of Osteoradionecrosis

Basic Studies

Several studies have been carried out to demonstrate the protective effect of HBO on osteoradionecrosis. Wang *et al* (1998) carried out experiments to test for a protective effect of HBO and basic fibroblast growth factor (bFGF) on bone growth. Control C3H mice received hind leg irradiation at 0, 10, 20, or 30 Gy. HBO-treated groups received radiation 1, 5, or 9 weeks before beginning HBO. The remaining

groups began bFGF ± HBO 1 or 5 weeks after 30 Gy. HBO treatments were given 5 days per week for 4 weeks at 2 ATA for 3 h/day. At 18 weeks control tibia length discrepancy was 0.0, 4.2, 8.2, and 10.7% after 0, 10, 20, and 30 Gy, respectively. HBO beginning in week 1, 5, or 9 following 10 Gy decreased these discrepancies to 2.0% ($p < 0.05$), 1.8% ($p < 0.05$), and 2.4% ($p < 0.05$), respectively. After 20 Gy, HBO decreased these discrepancies to 7.0% ($p = ns$), 4.9% ($p < 0.05$), and 3.6% ($p < 0.05$), respectively. At 30 Gy, HBO alone had no effect on bone shortening. bFGF improved tibia length discrepancy with or without HBO. At 18 weeks length discrepancies were 6.5% ($p < 0.05$) and 7.3% ($p < 0.05$), and after bFGF alone were 6.8% ($p < 0.05$) and 7.3% ($p < 0.05$) for treatment beginning in week 1 or 5, respectively. Tibial growth at 18 and 33 weeks following radiation were similar. This study showed that radiation effects on bone growth can be significantly reduced by HBO after 10 or 20 Gy, but not after 30 Gy. At 30 Gy bFGF still significantly reduced the degree of bone shortening, but HBO provided no added benefit to bFGF therapy.

HBO therapy was found to be effective in the treatment of complications of irradiation for cancer in head and neck area (Narozny *et al* 2005). Impact of perioperative HBO therapy on the quality of life of maxillofacial patients who undergo surgery in irradiated fields has been assessed in 66 patients (Harding *et al* 2008). The Head and Neck submodule identified significant improvements in teeth, dry mouth and social contact. It was recommended that adjunctive HBO should be considered for the treatment and prevention of some of the long-term complications of radiotherapy.

Osteoradionecrosis of the Mandible

Mandibular osteoradionecrosis is a late complication of radiotherapy for cancers of the head and neck, particularly of the oral cavity. Mandibular osteoradionecrosis is also the most frequently reported radiation injury – 235 of 378 patients (62.2%) in the series of Hart and Strauss (1986). This high frequency is because of the singularity of the blood supply running through the matrix of the bone and the proximity of the tumor to the mandible. Radiation decreases the number of osteoclasts and osteoblasts in the irradiated mandible, and if the mandible is fractured, the healing is delayed. In a normal mandible, after fracture, the alveolar processes remodel, and tooth sockets will heal in 9–12 months.

X-rays of the mandible in osteonecrosis show a variety of lesions including osteolysis and pathological fracture. In some cases, x-rays do not show any abnormalities and when present, the abnormalities do not necessarily correlate with the clinical severity of the disease. In the past, infection was considered to play a role in the pathogenesis of osteoradionecrosis, although it is now considered essentially a nonbacterial process. The following conventional treat-

ments have been used during the past 30 years on the assumption that osteoradionecrosis is an infection:

- Irrigation of the wound with a variety of solutions ranging from saline to hydrogen peroxide and other disinfectants
- Antibiotic therapy
- Superficial sequestrectomy

These treatments are obsolete now and HBO has an important role in the management of osteoradionecrosis of the mandible (Guernsey & Clark 1981, Patel *et al* 1989, Fattore & Strauss 1987). Of the 206 patients of Hart and Strauss (1986) who underwent treatment with HBO as an adjunct, 72% had an excellent result, 10% a good result, and 15% a fair response. The remaining 3% were failures.

There are some variations in the technique of combination of HBO with surgery. The Marx/University of Miami protocol (Marx & Johnson 1988) consists of three stages:

Stage I

This includes all patients having osteoradionecrosis of the jaw with three exceptions: cutaneous fistulae, pathological fractures, and radiological evidence of bone absorption at the inferior border of the mandible. Patients with these exceptions are allocated to stage III. Treatment of stage I includes daily HBO treatments at 2.4 ATA (90 min), wound care by saline rinses, no bone removal, and discontinuance of antibiotics. If improvement continues, ten further sessions of HBO are given. If there is no improvement, the patient is considered a nonresponder in stage I and moved to stage II.

Stage II

A local wound debridement is attempted to identify patients with only cortical bone involvement who do not require jaw resection. A transoral alveolar sequestrectomy is performed. If healing continues satisfactorily, ten further HBO treatments are given. If the wound dehisces, the patient is considered to be a nonresponder in stage II and is moved to stage III.

Stage III

The patient is given 30 HBO treatments followed by transoral partial jaw resection and a stabilization procedure (extraskelatal or mandibulo-maxillary fixation). A further ten HBO treatments are given and the patient is advanced to stage III-R (reconstruction).

Stage III-R

The emphasis in this stage is on early reconstruction and rehabilitation. Ten HBO sessions are given in the postoperative period and jaw fixation is maintained for 8 weeks.

Marx treated 268 patients over a period of 8 years using this protocol. Resolution of the lesions was achieved in 38 patients in stage I (14%), 48 patients in stage II (18%), and 182 patients in stage III (68%). Marx *et al* (1985) carried out a randomized clinical trial of HBO vs penicillin for prevention of radiation-induced osteoradionecrosis after tooth extraction in a high-risk population. One group received only penicillin before and after extraction; the other group received no antibiotics, but did receive HBO at 2.4 ATA for 20 daily sessions of 90 min each. One-half of the sessions were given before the extractions and the other half afterwards. The incidence of osteoradionecrosis was 29.9% in the antibiotic group and only 5.4% in the HBO group. The conclusion was that HBO should be considered as a prophylactic measure when postradiation dental care (e.g., tooth extraction) involving trauma to the tissues is necessary.

Mounsey *et al* (1993) carried out a retrospective analysis of 41 patients with osteoradionecrosis of the mandible treated at the Hyperbaric Chamber Unit of the Toronto Hospital and reported that 83% of these patients had a significant improvement. These authors concluded that HBO is of benefit in the management of these cases and that mild cases will heal with HBO alone but in severe cases surgery is necessary to remove the dead tissue. The authors recommended that such patients should receive dental evaluation, local wound care, and a strict oral hygiene. Diseased teeth should be removed prior to radiotherapy and any teeth that develop abscesses subsequently should be extracted in conjunction with prophylactic HBO.

Epstein *et al* (1997) carried out a study was to assess the long-term progress of 26 patients who experienced postradiation osteonecrosis of the jaw between 1975 and 1989. Of 26 patients who had been previously managed with HBO therapy as a part of their treatment for postradiation osteonecrosis of the jaw, 20 were evaluated to determine their current status of the condition: resolved, chronic persisting (unresolved), or active progressive (symptomatic). Two of 20 patients experienced recurrences of the condition. In one of these patients, surgical treatment was identified as the stimulus of postradiation osteonecrosis. In the other patient, the recurrence appeared to be related to periodontal disease activity. In 60% (12 of 20) of the patients, the condition remained resolved, improvement in clinical staging occurred in 10% (2 of 20) (from symptomatic to unresolved or resolved); and 20% (5 of 20) of the patients continued to demonstrate chronic persisting postradiation osteonecrosis at the end of the long-term follow-up period. This study supports the contention that postradiation osteonecrosis can occur at any time after radiation therapy, and that patients remain at risk up to 231 months after treatment of the cancer and probably indefinitely after radiation therapy. These findings also suggest that risk of second episodes of the condition after management of an ini-

tial episode is low. In addition, the follow-up study revealed that chronic nonprogressive postradiation osteonecrosis can remain stable without extensive intervention including combined HBO therapy and surgery.

Osteonecrosis of the Temporal Bone

Temporal bone is susceptible to the development of osteoradionecrosis because it is covered by a thin layer of skin, has a limited blood supply, and is composed mainly of compact bone. The latent period for the development of clinically manifest osteoradionecrosis of the temporal bone is 8 months to 23 years with an average of 8 years (Ramsden *et al* 1975). Surgical treatment involves removal of all necrotic bone.

Rudge (1993) treated a patient with osteoradionecrosis of the temporal bone using HBO as an adjunct and the result was complete resolution.

Osteoradionecrosis of the Chest Wall

There were 20 cases of osteonecrosis of the chest wall in the series of Hart and Strauss (1986). The osteonecrosis developed following radiation therapy for cancer of the breast, lung or mediastinum and involved the sternum and/or ribs. All the patients recovered.

Kaufman *et al* (1979) presented three cases of postradiation osteomyelitis of the chest wall that were treated successfully by a combination of HBO and surgery.

Osteoradionecrosis of the Vertebrae

Four cases of necrosis of the vertebrae in the series of Hart and Strauss (1986) were treated by HBO and minor debridements. All four patients recovered, and three had spontaneous fusions.

Management of Radionecrosis of CNS

Radiation Myelitis

Radiation myelitis of the cervical spinal cord was first reported more than 60 years ago following radiation therapy for pharyngeal cancer (Ahlbom 1941). The pathology of radiation injury usually involves interstitial tissue damage and microvascular endothelial injury causing thrombosis with secondary regional ischemia. Provision of HBO during the period of ischemia should, theoretically, minimize the effect of radiation injury. However, HBO has also been shown to potentiate the effects of radiation. One of the

practical problems is that adverse neurological effects of radiation may not manifest clinically for several months following exposure.

Poulton and Witcofski (1985) investigated the use of HBO in rats with radiation-induced myelitis. The animals were randomized into HBO-treatment and control groups. Eight weeks following radiation therapy, the animals in the treatment group were given HBO at 2.5 ATA for 30 min 5 times a week for 4 weeks. Serial neurological examinations did not show any benefit or harm as a result of HBO therapy.

Feldmeier *et al* (1993c) carried out an animal experimental study to investigate HBO as a treatment or prophylaxis for radiation myelitis. All animals received identical amounts of radiation. Group I received no HBO, group II began HBO at onset of myelitis, group III received HBO as prophylactic beginning 6 weeks after radiation, and group IV received HBO and radiation on the same day but following it after no less than 4 h. HBO consisted of 90 min sessions at 2.4 ATA for 20 daily treatments. All animals progressed to myelitis but it was least severe in group III and most severe in group IV.

Glassburn *et al* (1977) investigated the efficiency of HBO for established radiation myelitis. They reported 9 patients in whom radiation myelitis had appeared 5–21 months after receiving 400–6300 rads for a variety of tumors in or overlying the spinal cord. Patients were treated 2–5 times weekly for 2–30 min at 2.5–3.0 ATA. The total number of treatments ranged from 21 to 61. They concluded that 6 of the 9 patients improved as a result of therapy. Torubarov *et al* (1983) studied the cerebral hemodynamic changes under HBO in 23 patients with brain vascular pathology in the late period of radiation-induced disease. Clinical improvement was observed in all patients.

Hart and Strauss (1986) reported 10 patients (8 males and 2 females, average age 46 ± 8 years) who had radiation myelitis. The patients were given HBO at 2 ATA for 90 min twice daily for 2 weeks. Three patients with established neurological deficit did not show any response. Three patients who were treated within 1 year of onset showed cessation of progression of disease and slight improvement. Four patients who had symptoms for less than 6 months showed marked improvement in function. The authors concluded that HBO is useful in radiation myelopathy; however, patients should not be given treatment immediately following the radiation, but at least 2 months after the last radiation treatment.

In a retrospective analysis of 9 patients with radiation myelopathy treated with HBO, 6 (66%) were been stabilized or improved by HBO (Angibaud *et al* 1995). There are few case reports of use of HBO for radiation myelitis in recent years. One report describes a case of radiation myelitis with a progressive improvement in the clinico-radiologic picture following HBO that was documented by

MRI (Calabro & Jinkins 2000). Controlled studies are required to prove the value of HBO in this disease.

Radiation Encephalopathy

Radiation encephalopathy has been reported following radiation therapy for brain tumors and is sometimes difficult to differentiate from the recurrence or extension of the brain tumor. Hart and Strauss (1986) reported two patients with radiation-induced encephalopathy who were treated with a combination of vasodilators and HBO and showed marked improvement in cerebral function. Radiation-induced necrosis (RIN) of the brain is a complication associated with the use of aggressive focal treatments such as radioactive implants and stereotactic radiosurgery. Ten patients who presented with new or increasing neurologic deficits associated with imaging changes after radiotherapy received HBO treatments (Chuba *et al* 1997). Necrosis was proven by biopsy in eight cases. HBO was comprised of 20–30 sessions at 2–2.4 ATA, for 90–120 minutes. Initial improvement or stabilization of symptoms and/or imaging findings were documented in all ten patients studied and no severe HBO toxicity was observed. Four patients died, with the cause of death attributed to tumor progression. Five of six surviving patients were improved by clinical and imaging criteria; one patient was alive with tumor present at last follow-up. The authors concluded that HBO is an important adjunct to surgery and steroid therapy for RIN of the brain.

Two patients with arteriovenous malformations, who developed radiation encephalopathy following treatment with Gamma Knife, were treated by HBO at 2.5 ATA in sessions of 60 minutes per day (Leber *et al* 1998). This treatment was repeated 40 times in cycles of ten sessions. Both patients responded well to HBO, one lesion disappeared and the other was reduced significantly in size. No adjuvant steroids were given. Although these results provide evidence for the potential value of HBO in treating radiation encephalopathy, further experience will be needed to confirm its definite benefit.

Kohshi *et al* (2003) described the use of HBO therapy to manage radiation necrosis of the brain, which developed after two treatments with stereotactic radiosurgery to the same lesion. Treatment was continued with steroids alone for 2 months, but the patient started to deteriorate clinically and radiographically. Improvement started again following the resumption of HBO therapy.

Radiation-Induced Optic Neuropathy

Radiation-induced optic neuropathy (RION) is a devastating complication of radiotherapy to the head and neck. Cu-

mulative doses of radiation that exceed 50 Gy or single doses to the anterior visual pathway or greater than 10 Gy are usually required for RION to develop. RION has been reported years after external beam radiation therapy. Patients commonly presents with unexplained, painless visual loss in one or both eyes, visual field defects, pupillary abnormalities, and defective color vision. Various theories of pathomechanism implicate vascular occlusion, demyelination, free radical injury, direct damage to cellular DNA, and damage to the blood-brain barrier. MRI with or without contrast is an important diagnostic tool. Visual outcome is poor and there is no established treatment. Corticosteroids and free-radical scavengers showsome efficiency in treatment, especially in acute phases. Guy and Schatz (1986) suggested HBO treatment of RION. Roden *et al* (1990) treated 13 patients with RION using a combination of corticosteroids and HBO. Recurrence of tumor and other causes of loss of vision were ruled out by appropriate studies. There was no improvement of vision in any of these patients. Borruat *et al* (1993) and Liu (1992), however, have presented cases RION where visual recovery occurred after HBO therapy. Partial visual recovery from RION after HBO has been reported in a patient with Cushing disease treated with stereotactic radiosurgery of the pituitary galnd (Boschetti *et al* 2006).

Management of Radionecrosis of Soft Tissues

Delayed Radiation Injuries of the Extremities

Radiation injuries of the extremities usually present as nonhealing wounds within the radiation fields of previously treated skin cancer. Feldmeier *et al* (1998) have presented their experience with 17 such patients. They were treated in a multiplace chamber at 2.4 ATA daily and wound care was maintained. Eleven of these patients had complete resolution of the wounds, one had improvement but not complete healing while 4 failed to heal and went on to have amputations. The success rate of HBO in this setting was 65% and non-responders to HBO had a 80% rate of going on to amputations. It is thus important that these patients should have an adequate trial with HBO as the first line treatment.

Soft Tissue Necrosis of the Head and Neck

Radiotherapy, which is often used for cancer in the head and neck, leads to damage of tissue cells and vasculature. Surgery in such tissues has an increased complication rate, because wound healing requires angiogenesis and fibroplasia

as well as white blood cell activity, all of which are jeopardized. HBO raises oxygen levels in hypoxic tissue, stimulates angiogenesis and fibroplasia, and has antibacterial effects. There were 48 patients with soft tissue necrosis of the head and neck in the series of Hart and Strauss (1986). All of these presented after operative procedures with breakdown. With the exception of one lethal aspiration, all the patients improved.

In a consecutive retrospective study, 15 patients with soft-tissue wounds without signs of healing after surgery in full-dose (64 Gy) irradiated head and neck regions were treated with HBO and adjuvant therapy (Neovius *et al* 1997). The patients in this study were also compared with patients examined in an earlier study, with corresponding wounds treated without HBO. The healing processes seemed to be initiated and accelerated by HBO. In the HBO group, 12 of 15 patients healed completely, 2 patients healed partially, and only 1 patient did not heal at all. There were no life-threatening complications. In the reference group, only 7 of 15 patients with corresponding wounds without signs of healing eventually healed without surgical intervention, and 2 patients had severe postoperative hemorrhage, which in one case was fatal. Evaluation of results supports the hypothesis that HBO therapy has a clinically significant effect on initiation and acceleration of healing processes in irradiated soft tissues.

Radionecrosis of the Larynx

Radiation therapy is the treatment of choice for early stages of laryngeal cancer and larynx is often included in the field of radiation of head and neck cancer. Postradiation edema of the larynx usually resolves spontaneously but occasionally persists as long as 6 months. Laryngeal radionecrosis is an uncommon complication of radiotherapy for carcinoma of the head and neck. The interval between conclusion of radiation therapy and development of radionecrosis ranges from 3 to 12 months. Neither computed tomography nor magnetic resonance imaging differentiate between necrotic tissue and recurrent tumor. Tissue ischemia and hypoxia play an important role in its pathogenesis. This is a debilitating disease with pain, dysphagia, and respiratory obstruction. Biopsy is required to differentiate it from recurrent cancer. The pathological changes are fibrosis, endarteritis, and chondroradionecrosis. Tracheostomy and laryngectomy is required in some cases.

Chandler's grading system (Feldmeier *et al* 1993b) is a useful guide to the evaluation of the therapy of laryngeal necrosis. It is summarized as follows:

- Grade 1: Slight hoarseness. Laryngeal edema and telangiectesia.

- Grade II: Moderate hoarseness. Slight impairment of vocal cord mobility and moderate edema.
- Grade III: Severe hoarseness with dyspnea and dysphagia. Severe impairment of cord mobility.
- Grade IV: Respiratory distress. Fistula, fixation of the skin to the larynx, laryngeal obstruction

Humidification, broad spectrum antibiotics, steroids, and hyperbaric oxygen, with or without surgery, are successful in many cases. Ferguson *et al* (1987) presented 8 patients with advanced radionecrosis of the larynx who were treated with adjuvant HBO therapy. Four of these patients were Chandler's grade IV laryngeal necrosis. Signs and symptoms of radionecrosis were markedly ameliorated in 7 of the 8 patients. Only one patient required laryngectomy. As compared with a previous series of cases where HBO was not used, there was a definite improvement of the outcome in these cases treated by HBO therapy as an adjunct.

Feldmeier *et al* (1993a) treated 9 patients with laryngeal necrosis using HBO. Eight of these patients were Chandler's grade IV and the ninth was grade III. All the nine patients were able to maintain their voice until death or last follow up. All patients with tracheostomies could be decannulated and the fistulae were closed. The authors recommended HBO as a therapeutic option whenever laryngeal necrosis occurs and there is a chance to save the larynx.

Delayed Radiation Injuries of the Abdomen and Pelvis

Radiation therapy is less commonly applied for malignancies of the abdomen but is still used for some cancers of the pancreas, biliary tree, stomach and colon. Radiation doses are limited due to poor tolerance of normal organs located in the abdomen. Whole abdomen radiation for ovarian cancer with local spread can have about 20% risk of complications. The most serious complications usually occur after a period of 6 months or longer and result from vascular compromise and hypoxia secondary to reactive fibrosis in the irradiated tissue. Some of these complications require surgical interventions. Feldmeier *et al* (1996) have reviewed 44 patients with radiation injury involving abdomen and pelvis and 41 of these were available for follow-up examination. Twenty-six of these patients healed, six failed to heal and nine patients had inadequate HBO therapy (less than 20 treatments). Overall, the success rate in patients receiving at least 20 treatments was 81%.

Clinical improvement of malabsorption due to radiation enteritis has been reported following HBO therapy (Neurath *et al* 1996). Hamour and Denning (1996) reported a patient who developed severe diarrhea with blood and

pain in the rectum following post-operative radiation therapy for uterine cancer. She was advised to have a colostomy but declined. After 98 hours of HBO treatments (2.5 ATA) over a period of four weeks, she improved and the rectal ulceration decreased in size until it healed completely two months later. The patient did not have any recurrence of these symptoms.

Radiation-Induced Hemorrhagic Cystitis

This is an adverse effect of therapeutic radiation administered for a variety of pelvic malignancies. Clinical features are:

1. Recurrent hemorrhage (hematuria)
2. Urinary urgency
3. Pain

Bladder biopsy in these cases shows the following:

1. Mucosal edema
2. Vascular telangiectasis
3. Submucosal hemorrhages
4. Obliterative endarteritis
5. Smooth muscle fibrosis

It is a progressive disease and does not resolve spontaneously. Conventional treatment of this complication has included the following modes of treatment:

- Intravascular instillation of formalin, alum, and silver nitrate
- Systemic use of steroids and aminocaproic acid (inhibitor of fibrinolysis)
- Antibiotics
- Cauterization of bleeding vessels
- Bilateral ligation of the hypogastric arteries

Most of these approaches treat symptoms but none of these promote healing and may even have undesirable side effects. Because these complications are partially due to endothelial damage as well as to decreased vascularity and oxygenation to pelvic tissues, HBO may be able to improve oxygenation and induce angiogenesis in damaged organs, resulting in recovery from radiation injury. Rijkmans *et al* (1989) treated 10 patients with radiation-induced cystitis with HBO at 3 ATA (90-min sessions/day, 5 days/week) for an average of 20 sessions. In 6 patients hematuria stopped after 12 sessions of HBO. In another 4 patients where there was only partial resolution of hematuria, residual tumor was found in the bladder mucosa and was better defined after resolution of the edema of the surrounding tissue. The tumor was resected in these patients.

Hart and Strauss (1986) presented 15 patients with radiation cystitis, 11 of whom were relieved of symptoms of tenesmus and hematuria by a combination of HBO and surgery.

Weiss and Neville (1989) treated each of their 8 patients suffering from radiation-induced cystitis with a series of 60 HBO sessions (2 h at 2 ATA daily). They were able to document the improvement in 7 of these patients by cystoscopy. The hypervascularity of the bladder wall was diminished. The authors stated that the symptomatic relief was accompanied by a significant reversal of tissue injury. Clinical remissions were an average of 24 months (range 6 to 43 months). Only one patient failed to respond. The authors recommended HBO as the primary treatment for patients with symptomatic radiation-induced hemorrhagic cystitis.

Other cases of radiation-induced cystitis treated successfully by use of HBO have been reported by other authors (Shoenrock & Cianci 1986, Velu & Myers 1992, Kindwall 1993, Nakada *et al* 1992, Shameem *et al* 1992, Morita *et al* 1994). The largest series is that of Norkool *et al* (1993) who treated 14 patients with radiation-induced cystitis using HBO at 2.4 ATA for 90 min daily sessions for an average of 28 treatments per patient. There was complete resolution or marked improvement in 10 of these (74%). Of the 4 patients with poor outcome, 3 had recurrence of malignancy that was not present before HBO treatment. The cost of HBO therapy compared favorably with that of conservative treatment.

In conclusion, HBO has been shown to have a favorable effect on the course of radiation-induced cystitis as observed in 50 of the 63 published cases and several other cases which have not been reported. There is a difference in pressure used. It appears that use of 2.4 ATA instead of 2 ATA reduces the number of treatments from about 60 to about 30. A prospective (but not controlled) study has shown beneficial effect of HBO on radiation cystitis (Bever *et al* 1995). There is a lack of randomized trials to definitively demonstrate the effectiveness of HBO for cystitis. Concern still exists regarding the durability of the beneficial effects.

Radiation Proctitis

Chronic proctitis is a well-known complication of therapeutic irradiation. Most patients had previously been treated with radiotherapy for prostate carcinoma. Radiation-induced proctitis is a difficult clinical problem to treat and will probably become more significant with the rising incidence of diagnosis of prostate cancer. Patients with proctitis mainly suffer from bleeding, diarrhea, incontinence, and pain.

Charneau *et al* (1991) reported a case of a male patient

suffering from severe radiation-induced hemorrhagic proctitis which healed after HBO therapy. Williams *et al* (1992) carried out a prospective observational study on 14 patients with radiation-induced soft tissue necrosis following treatment of pelvic malignancy and after the wounds had failed to heal after 3 months of conservative therapy. All of the patients received 15 courses of HBO. All those with radiation necrosis of vagina or rectovaginal fistula healed. There was only one treatment failure.

Warren *et al* (1997) treated 14 patients with chronic radiation-induced proctitis with HBO. Nine patients were treated in a monoplace chamber at 2 ATA, and five patients were treated at 2.36 ATA. Eight patients experienced complete resolution of symptoms and one patient had substantial improvement for a total response rate of 64%. Follow-up ranged from 5 to 35 months. Five patients (36%) were classified as non-responders.

Three experienced significant improvement during treatment but relapsed soon after therapy was discontinued, whereas two had no symptomatic improvement. Responders who had sigmoidoscopy after therapy showed documented improvement whereas no non-responders showed improvement. The authors concluded that HBO therapy should be considered in patients with chronic radiation proctitis.

In more than half of the patients with radiation proctitis, symptoms partially or completely resolved after HBO treatment (Woo *et al* 1997). HBO should be considered in the treatment of radiation-induced proctitis. Further prospective trials with strict protocol guidelines are warranted to definitively demonstrate the effectiveness of HBO for proctitis.

Effect of HBO on Cancer Recurrence

Because there may be residual cancer in some of the patients treated for radiation necrosis, there is some concern that HBO may promote cancer growth or recurrence. Eltorai *et al* (1987) presented a historical review of the effects of HBO on malignancy. They reported 3 cases of occult carcinoma that manifested clinically after HBO was started and presumably led to the proliferation of the tumor in all 3 cases. The authors considered HBO therapy to be contraindicated in malignancy. There is no evidence to substantiate this view.

Squamous cell carcinoma transplanted in mice neither progresses or regresses when the animals are exposed to HBO (Sklizovic *et al* 1993). Other studies suggest that HBO may even have an inhibitory effect on cancer growth (Ehler *et al* 1991, Headley *et al* 1991, Mestrovic *et al* 1990). McMillan *et al* (1989) studied the effect of HBO on dimethylbenzanthracene-induced oral carcinogenesis in an animal model. The group that received simultaneous HBO had fewer

tumors but these were larger than those in the non-HBO group. They concluded that HBO has a tumor-suppressive effect during the induction phase of oral carcinoma and appears to have a stimulatory effect during the proliferative phase. In a survey of this topic, majority of the hyperbaric practitioners who responded, did not consider HBO to have cancer-promoting or cancer-accelerating properties (Feldmeier *et al* 1993b).

Feldmeier *et al* (1994) reviewed the pertinent literature to answer the question: Does hyperbaric oxygen have a cancer-causing or -promoting effect? Several of the studies showed a positive effect of HBO in suppressing tumor growth whereas other studies failed to demonstrate this effect. One explanation of this difference is that generation of free radicals by HBO may diminish superoxide dismutase and affect the susceptibility of tumor cells to HBO (Mestrovic 1996).

Conclusions

Radiation wounds are difficult to treat and in the past there have been few non-surgical options. Now, there is considerable evidence of the beneficial effect of HBO on radiation necrosis and it has become a useful adjunct to surgery. Among the bony structures, the effect on osteoradionecro-

sis of the mandible is most striking. Among the soft tissues, the effect on laryngeal necrosis is impressive. The effect on the radionecrosis of the neural tissues other than the brain is not striking.

There are no controlled studies to prove the efficacy of HBO in radionecrosis. Apart from the variations in clinical presentation, there is difficulty in controlling other methods of treatment.

Feldmeier and Hampson (2002) reviewed 74 publications reporting results of applying HBO in the treatment or prevention of radiation injuries and appraised these in an evidence-based fashion. All but seven of these publications report a positive result when HBO is delivered as treatment for or prevention of delayed radiation injury. These results are particularly impressive in the context of alternative interventions. Without HBO, treatment often requires radical surgical intervention, which is likely to result in complications. Other alternatives including drug therapies are rarely reported, and for the most part have not been the subject of randomized controlled trials. Based on this review, HBO is recommended for delayed radiation injuries for soft tissue and bony injuries of most sites.

Growth factors show promise in the management of chronic irradiated tissues and it would be worthwhile to investigate the effect of combination of HBO with growth factors.