

# wound healing perspectives®

A CLINICAL PATHWAY TO SUCCESS

VOLUME 7 NO. 2 2010

→ Osteoradionecrosis

## Treating and preventing osteoradionecrosis

Osteoradionecrosis is the end-stage of delayed radiation injury that most commonly occurs in the mandible when it's been previously irradiated. This tissue is hypoxic, hypocellular, and hypovascular. A simple biopsy or tooth extraction can create a wounding incident that puts an extreme metabolic and vascular demand on already-compromised tissue. And the risk of tissue breakdown and non-healing wounds increases as time passes. The wounds that occur in the irradiated tissue are one of the clearest indications for HBO treatment to prevent and manage problem wounds. Additionally, intractable pain, nutritional deficiencies, pathologic fractures, and oral and cutaneous fistulas are just some of the complications patients frequently face.

Finding and treating the underlying cause of these wounds is a great service to our patients and their families. This issue of Wound Healing Perspectives focuses on the best-practice methods of treating and preventing osteoradionecrosis – I hope you find it helpful.

Sincerely,



Katy Rowland, RN, MBA  
Chief Clinical Officer  
National Healing Corporation

## Causes and incidence of radiation injuries

The National Cancer Institute reports that the survival rate for all cancers diagnosed between 1996-2004 is 66%, up from 50% from 1975-1977. The American Cancer Society (ACS) attributes the increase in survival rate to the early diagnosis of certain types of cancer and improvements in treatment. Even so, about 1.5 million people will be diagnosed with cancer in 2009. Additionally, the National Cancer Institute estimates that millions more people are living with the effects of cancer or have been cured.

The ACS lists radiation therapy as one of the most common cancer treatments and states that it is used in more than half of all cancer cases, such as head and neck cancers, prostate cancer, and breast cancer. There are two types of radiation injury: acute dermatitis, which frequently sets in early and is treated conservatively with balms and ointments; and serious radiation complications which can occur in up to 5% of those patients receiving



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### Highlights Inside:

Osteoradionecrosis.....	2
Preventing osteoradionecrosis.....	2
Hyperbaric oxygen chambers.....	3
Evaluating the quality of irradiated bone.....	3
HBO vs. penicillin.....	4-5
The Marx Protocol for ORN therapy.....	4
Treating osteoradionecrosis.....	5
Indications for HBO.....	6-7
Osteonecrosis, bisphosphonates..	4
maxillofacial wounds	
HBO is a cost effective treatment for.....	8

continued on page 3

# Osteoradionecrosis

Osteoradionecrosis (ORN) is simply defined as “exposed bone in a field of radiation that has failed to heal either spontaneously or with treatment for at least six months.” (Johnson, et al, 1994) Both the soft tissue and underlying bone are involved. The soft tissue wound is an “ulcerative loss of overlying mucosa or skin that exposes the bone beneath.” The bone is not viable and may or may not show osteolysis. ORN is most commonly found in the mouth. Pasquier, et al, in a 2004 literature review in *Radiotherapy and Oncology*, found the reported incidence of ORN ranges from 1-27.5%. Comparison of the different reports is difficult due to differences between the studied populations (radiotherapy alone, technique of radiation, brachytherapy, post-operative radiotherapy, policy of dental management, etc.). Overall, the incidence has decreased over the last 20 years.”

Following irradiation, the tissue becomes hypovascular, hypocellular, and hypoxic. The tissue then begins to break down either spontaneously or as a result of trauma. Ultimately, the area becomes a non-healing wound, where the metabolic demands

surpass the body’s ability to provide for them.

Micro-organisms begin to impact the surface of the exposed bone in the mouth. These factors combine to make ORN a problem of wound healing rather than of infection – closely related to a diabetic ulcer of the lower extremities. (Marx, 1983)

The mandible is the most common site of these wounds primarily because the bone is poorly vascularized due to its density, but also because teeth are present. Since radiation is successfully used to treat many types of head and neck cancer caused by tobacco use, the area is also a common site of irradiation.

Risk factors for ORN include the following:

- Inadequate post-dental extraction healing time before radiation therapy;
- Traumatic extractions within irradiated bones;
- Alcohol and tobacco abuse; and
- Nutritional factors. (Stofka, 1993)

ORN can occur at any time after a patient receives radiation therapy to the head or neck. The risk increases with time



because the degenerative process is ongoing. Delayed complications, seen later than six months after treatment, can develop many years after initial exposure. (Neal, 2000) While the incidence of complications like these is low (on the order of 1-5%), fully half of these patients are likely to have post-operative complications.

Complications that result from ORN include intractable pain, trismus, nutritional deficiencies due to the inability to ingest food, pathologic fractures, oral and cutaneous fistulas, and the loss of large areas of soft tissue and bone. Drug dependency is also a frequent challenge for these patients. Patients suffer the psychological stigma of severe facial deformities and having a non-healing wound. They also often lose time from work and family. (Johnson, et al, 1994)

## Preventing Osteoradionecrosis

Given the pain, debilitation, and expense involved in treating ORN, any prevention opportunity should be seized. Patients considering radiation therapy of the head or neck should seek a pre-radiation dental consultation to optimize oral health and prevent dental work after the radiation treatment. Preventive HBO is necessary when post-irradiation dental care involving trauma to the mandible is needed. Marx’s suggested protocol for prevention therapy is 20 pre-surgical HBO treatments followed by 10 post-surgical treatments.

Feldmeier’s systematic review (2002) includes three published reports (two case series and one randomized controlled trial) that suggest HBO prevents mandibular osteoradionecrosis (ORN). There was a collective incidence of ORN in 4.5% of patients who received HBO as part of their therapy. ORN occurred in 29.9% of patients in the single control group that Marx tracked.

# Hyperbaric oxygen chambers

Monoplace hyperbaric oxygen chambers are used in all National Healing Wound Centers when needed to promote healing in patients with osteoradionecrosis.

These HBO chambers are designed for use in clinical environments requiring in-chamber transcutaneous oxygen monitoring, patients air-breaks, or pre-assessment with TCOM and skin perfusion tests.

These HBO chambers were designed with safety in mind. Both the chamber

and stretcher are grounded. A patient grounding strap is provided. Each HBO chamber has a patient-activated call system in addition to continuous audio monitoring via the two-way communication system.

All Wound Healing Center clinical staff are specially trained at the National Healing Institute's Wound Care and Hyperbaric Oxygen course in the theory and practice of using HBO chambers. Contact your Wound Healing Center today to arrange a tour of the center.



## Causes and incidence of radiation injuries - cont'd

therapeutic radiation requiring more advanced care. (Feldmeier, 2002)

Following initial tumor radiation, blood vessels degenerate. This progressive process continues throughout the patient's life and blood supply continues to diminish. In the event of even minor trauma, healing is impaired due to this ischemic change in tissue. These problems are often discovered long after the radiation therapy is complete –

sometimes several years later. The most common sites of radiation injuries are the head, neck, genitourinary area, and bowel. Unresolved serious delayed radiation injuries cause death under certain circumstances and certainly decrease quality of life in most instances. (Feldmeier, 2002)

The methodology of treating radiation injuries has changed dramatically over time. It was once believed that irradiated tissue will

gradually revascularize and improve with time. This caused physicians to delay reconstruction and tooth extractions to take advantage of these changes. It is now known that delaying treatment longer than six months will lead to serious complication such as soft tissue and bone necrosis due to decreased vascularity, less tissue perfusion, and more fibrosis. Decreased tissue perfusion can lead to a greater risk for healing complications.

## Evaluating the quality of irradiated bone

X-ray and computed tomography (CT) are useful to detect localized osteolytic processes. MRI is better to view inflammation in soft tissues and tumor infiltration in bone. Selective angiography of the craniofacial arteries can give information about local vascularity. (Granström, 1992)

The Centers for Medicare and Medicaid Services (CMS) require the following documentation to approve payment for HBO therapy for patients with ORN:

- Documented date and anatomical site of prior radiation treatments with documentation of fracture or resorption of bone, and radiographic studies, if available
- Diagnosis from referring physician
- Debridement or resection of non-viable tissue with antibiotic coverage

# The Marx Protocol for ORN therapy

Robert E. Marx, DDC, is chief of oral and maxillofacial surgery at the University of Miami Miller School of Medicine. He developed the Marx Protocol, the standard of care to prevent and treat ORN, in 1983. His current clinical interests are benign and malignant tumor surgery and reconstructive surgery. His current research interests are cancer research and wound healing and growth factors.

- **Stage 1:** all patients with ORN receive 30 HBO treatments at 2.4 ATA for 90 minutes each. Wound care is maintained and antibiotics are usually discontinued. The wound is re-evaluated after 30 treatments. If improvement is shown (amount of exposed bone decreases, resorption, spontaneous sequestration, or softening of exposed bone), the patient received 10 more treatments. If there is no response, the patient proceeds to Stage II as a non-responder.
- **Stage II:** local surgical debridement is completed to identify patients with superficial bone involvement who don't need jaw resection. All necrotic bone is removed to a base of bleeding bone with minimal periosteal reflection. If healing progresses well, 10 more treatments are completed, if the wound breaks down the patient is advanced to Stage III as a non-responder.
- **Stage III:** the patient undergoes a transoral partial jaw resection. The margins of the resection are determined by the presence of bleeding bone at the time of surgery. Any reconstruction that is needed to repair tissue deficiencies or fistulas should be performed at this time. HBO is immediately continued for

10 post-operative treatments. Prosthetic rehabilitation can begin three months after the reconstruction is complete. Soft tissue surgery can be performed one month after fixation removal. (Patients with pathologic fractures, fistulas, or radiographic evidence of osteolysis to the inferior border begin at Stage III.)

A systematic review of the literature by Feldmeier (2002) found 13 reports on the use of HBO in treating patients with ORN. Combining all of the reported cases provides a total of 371 cases of mandibular ORN.

Improvement was reported in 83.6% or 310 cases. Feldmeier points out that "although resolution would be a better end point, hyperbaric oxygen was not combined with aggressive extirpation of necrotic bone or with surgical reconstruction of bony discontinuity, especially in the earlier reports." Additionally, Neal comments that "anecdotally, surgeons dealing with post HBOT patients comment on how 'bloody' they are at surgery, compared to those not treated with HBOT. This increased vascularity improves the chance of successful surgical intervention."

Studies carried out at the hyperbaric unit at the U.S. Air Force School of Aerospace Medicine demonstrate that the pO<sub>2</sub> in the radiated area will rise to approximately 80% of normal after 18 to 30 treatments. It plateaus at this level, but this is sufficient to make surgery and even grafting in the radiated area possible. (Kindwall, 1992)

## HBO vs. penicillin

In 1985, Marx, et al, published a randomized prospective clinical trial comparing HBO and penicillin in the Journal of the American Dental Association (JADA). Here's what they reported:

- The pathogenesis of ORN has been shown to be a radiation-induced, non-healing, and hypoxic wound rather than an osteomyelitis of irradiated bone, establishing a scientific basis for using HBO in the treatment of ORN. HBO creates an environment where tissue angiogenesis in hypovascular irradiated tissue is induced by intermittent high oxygen tissue levels.

*continued on page 5*



# Treating osteoradionecrosis

Tooth extractions in the previously radiated jaw accounts for 89% of all trauma-induced cases of mandibular radionecrosis. Today's typical course of treatment for ORN is based on the concept that Marx presented in 1983. This treatment is designed to support the injured living tissue and surgically remove the non-living tissue. Wound repair can then proceed to resolve the disease. (Johnson, et al, 1994)

Conservative measures are often the first stage of treatment. In most series such treatment consists of local application of antiseptic, analgesics if necessary, oral hygiene, systemic antibiotics, possible sequestrectomy, and smoothing of bony protrusions. These measures result in healing 15-100% of the cases without the adjunct application of HBO, however, on average it takes several months before improvement occurs. Mandibular resection is necessary in 12-40% of the patients initially treated with conservative measures without HBO. (Pasquier, et al, 2004)

When teeth must be extracted due to radiation caries, subsequent mandibular radionecrosis can be avoided in 92% of cases by following the Marx Protocol to add HBO to the treatment plan. The patient's response or lack thereof to HBO is the main indicator for surgery. When the physician can differentiate the dead bone from merely compromised bone, the dead bone can be surgically resected. One study completed in the 1970s that didn't use HBO or surgery found that 92% of patients (41/45) were non-responders.

In 2004, Bui, et al., published a study in the International Journal of Radiation Oncology Biology Physics that showed "hyperbaric oxygen is a safe and effective treatment modality offering durable relief in the management of radiation-induced osteoradionecrosis either alone or as an adjunctive treatment. Radiation soft tissue necrosis, cystitis, and proctitis also seemed to benefit from HBOT, but the present study did not have sufficient numbers to reliably predict long-term response."



This conclusion was based on retrospective analysis of 75 subjects (of the original 105 eligible patients, 30 had died or could not be contacted); of whom 45 completed a questionnaire documenting the severity of their symptoms. Specific results were:

- Principal presenting symptoms improved after HBOT in 75% of head-and-neck, 100% of pelvic, and 57% of "other" subjects (median duration of response of 62, 72, and 68 weeks respectively).
- Bone and bladder symptoms were most likely to benefit from HBOT (response rate, 81% and 83% respectively).
- Relapse incidence was low (22%) and minor HBOT-related complications occurred in 31% of patients.

## HBO vs. penicillin

- HBO-induced angiogenesis becomes measurable after eight sessions, rapidly progresses to a plateau at 80% to 85% of non-irradiated tissue vascularity by 20 sessions, and remains at that level without further improvement with additional HBO. Patients who were restudied at one, two, and three years after their HBO therapy had TCPO2 levels at or within 90% of the values recorded just after treatment. There was no evidence of a regression of the tissue angiogenesis induced by HBO.

# Osteonecrosis and bisphosphonates

## Indications for HBO



Many commercial insurers have approved reimbursement for HBO therapy when the following diagnoses are made:

- Air or gas embolism
- Carbon monoxide poisoning (complicated by cyanide poisoning)
- Crush injury
- Compartment syndrome
- Acute traumatic ischemia
- Decompression sickness
- Enhancement of healing in selected problem wounds
  - Arterial
  - Diabetic
  - Post-operative
  - Pressure
  - Traumatic
  - Venous
  - Any non-healing wound

*continued on page 7*



*Dr. Robert Marx, Chief of Oral and Maxillofacial Surgery at the University of Miami Miller School of Medicine.*

***Recently, Dr. Robert Bartlett, Senior Medical Advisor for National Healing, spoke with Dr. Robert Marx about osteonecrosis caused by bisphosphonates. Here are the highlights of their conversation:***

Osteonecrosis caused by the use of intravenous and some oral bisphosphonates is a relatively new phenomenon. These osteoporosis drugs, such as Zometa® (zoledronic acid) and Fosamax® (alendronate), can cause chemical toxicity which leads to non-healing exposed necrotic bone in the maxillofacial region. Recognizing and preventing Biphosphonate Osteo-Necrosis of the Jaw (BRONJ) early can help preserve quality of life.

The definition of osteonecrosis is exposed bone with no nerve endings. Patients will recognize exposed bone and complain of a rough feeling in their mouths. The pain associated with

osteonecrosis comes from secondary infections that set in on the exposed bone. Osteonecrosis is not caused by an infectious disease but rather is the result of chemical toxicity.

There are two primary groups of patients at risk for BRONJ: individuals who have or had multiple myeloma or breast cancer and received at least four doses of IV Zometa, over any time frame since the half-life of this drug is more than 11 years in the bone, and individuals who take oral Fosamax, which is commonly taken daily at twice the dose of Boniva® and Actonel®.

***Recognizing and preventing Biphosphonate Osteo-Necrosis of the Jaw (BRONJ) early can help preserve quality of life.***

■ IV bisphosphonate patients: osteonecrosis in these patients is not resolvable short of major surgery. The American Association of Oral and Maxillofacial Surgeons recommends palliative care, intermittent antibiotics, and an antiseptic mouthwash to maintain these patients functional, infection-free, but with exposed bone. Twenty-five percent with advanced presentation such as a pathologic fracture also require antibiotics and a jaw resection.

■ Oral bisphosphonate patients: osteonecrosis in these patients is much less severe and can be treated to resolution with relatively minor surgery plus a backbone of a drug holiday of 6-9 months to allow a rebound effect so that necrotic bone can be sequestered or effectively debrided. Research has shown that osteoporosis levels are not materially impacted by drug holidays of as long as five years. Dentists and primary care physicians working closely together ensures a strong outcome.

HBO therapy, while very useful in the case of osteoradionecrosis due to the oxygen gradient deficit caused by radiation, is not as useful in osteonecrosis caused by bisphosphonates which is a chemical toxicity to bone. Since HBO does have a positive effect on the not-yet dead bone and tissue, it supports healing but doesn't make as large a difference as it does in radiation patients.

# Advanced wound care therapies in oral and maxillofacial wounds

*Dr. Bartlett also spoke with Dr. Marx about the applications of advanced wound care therapies for oral and maxillofacial wounds. Here's what Dr. Marx had to say:*

Platelet-rich plasma (PRP) is used for hard-to-heal patients, for example smokers, diabetics, the elderly, and those who've had radiation therapy. It is frequently used in combination with bone grafts to accelerate the bone graft healing. PRP is also used for skin grafts at the donor site and the recipient site to improve the healing rate and reduce scar tissue formation.

An emerging growth factor clinical application is the use of recombinant human bone morphogenetic protein (BMP) in conjunction with PRP to regenerate large amounts of bone that BMP alone could not do. The classic tissue engineering triangle calls for a signal (BMP), a matrix (PRP), and cells (bone marrow or PRP). When BMP is used alone, the matrix components (fibrin) are missing so the outcomes weren't as strong.

Biologicals are also used to treat oral and maxillofacial wounds. Apligraf® is used as a substitute for skin grafts in tongue cancers. Research combining alginate

bone with BMP and PRP to enable in situ bone regrowth has produced very good clinical outcomes.

*Dr. Robert Bartlett is the Senior Medical Advisor for National Healing Corporation, an Adjunct Professor of Surgery, the Ohio State University, and a 1980 Magna cum Laude graduate of the University of South Alabama, School of Medicine. Dr. Bartlett is certified in Wound Care, Hyperbaric Medicine and Emergency Medicine. He is the Editor in Chief and founding member for the creation of two physician certification exams; one for Hyperbaric Medicine and the other for Wound Care. Dr. Bartlett is also a Diving Medical Officer with the National Oceanic and Atmospheric Administration and is the past President of the American College of Hyperbaric Medicine.*



*Dr. Robert Bartlett, Senior Medical Advisor  
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## Indications for HBO cont'd



- Clostridial myositis and myonecrosis (gas gangrene)
- Exceptional blood loss (anemia)
- Intracranial abscess
- Necrotizing soft tissue infections
- Refractory osteomyelitis
- Delayed radiation injury
  - Soft tissue radionecrosis
  - Bony necrosis (osteoradionecrosis) grafts and flaps
- Thermal burns
- Central retinal artery occlusion intercranial access

**QUESTIONS OR COMMENTS?**

Contact Erica Park at 888.332.0202 or Erica.Park@nationalhealing.com

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# HBO is a cost effective treatment for ORN

Marx began to study the cost-effectiveness of combining HBO and surgery known as the Marx Protocol in treating ORN in 1984. This table shows that cost analysis in 1991 dollars. The combination of HBO and surgery has a 100% resolution rate and holds costs to less than one-quarter that of surgery alone and half that of HBO alone.

Treatment	Number of Patients	Average One Year Cost	Average Total Costs	Resolution Rate
Non-HBO	116	\$47,000	\$162,000	10%
HBO Without Surgery	88	\$40,000	\$83,000	18%
Marx-UM Protocol	492	\$49,000	\$49,000	100%
Marx-UM Protocol Used in Private Practice	112	\$45,000	\$45,000	100%

**UM=UNIVERSITY OF MIAMI**  
**COST ANALYSIS OF 300 CASES OF OSTEORADIONECROSIS IN U.S. DOLLARS (JANUARY 1, 1991), JOHNSON, ET AL, 1994. UPDATED APRIL 2004 IN A PRESENTATION IN BOYNTON BEACH, FL.**

## CONSIDER REFERRING YOUR PATIENTS TO A WOUND HEALING CENTER FOR ADVANCED CARE WHEN:

- They complain of exposed bone and pain in the mouth
- Your chairside evaluation shows any bone behind skin that cannot grow hair or is missing salivary or sweat glands
- They have a history of base-of-tongue carcinoma and have had radiation therapy as a treatment because the most common place to develop ORN is in the posterior mandible molar region
- They smoke
- They have diabetes