

Osteoradionecrosis

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ABSTRACT

Osteoradionecrosis (ORN) is a major complication of surgery or trauma in previously irradiated bone. This condition is often painful, debilitating and may result in significant bone loss. ORN of the mandible is the commonest site in patients who receive radiotherapy for head and neck cancer because of the relatively poor vascularization in this area. Risk factors include the total radiation dose, modality of treatment, fraction size and dose rate, oral hygiene, timing of tooth extractions as well as the continued use of tobacco and alcohol. Conversely, steroid use before or after radiation may have a protective effect related to the inhibition of the initial inflammatory phase of ORN. The management of this side effect is difficult and can result in bone or soft tissue loss, affecting the quality of life. The recommended treatment guidelines are irrigation, antibiotics, hyperbaric oxygen therapy and surgical techniques, including hemimandibulectomy and graft placements.

Keywords: Osteoradionecrosis, Radiotherapy, Hyperbaric oxygen therapy, Fibroatrophic mechanism.

INTRODUCTION

Amid the growing armory of new and developing therapies, the founding staples of head and neck malignancy, radiotherapy (RT), remains widely in use as one of the primary modalities of treatment or adjuvant to surgery, in conjunction with chemotherapy or as palliative treatment for last-stage tumors. High dose of radiotherapy often has serious effects on soft and hard tissues adjacent to neoplasm: Mucositis, atrophic mucosa, xerostomia and radiation caries are common. Because of its mineral composition, bone absorbs more energy than soft tissue and is more susceptible to secondary radiation. This leads to a complication termed as osteoradionecrosis (ORN). ORN is defined as exposed irradiated bone tissue that fails to heal over a period of three months without a residual or recurrent tumor.^{1,2} The incidence of ORN in the head and neck region ranges from 1 to 37.5%,³ with the range of 5 to 15% being most commonly reported.⁴

PATHOGENESIS

The pathogenesis of osteoradionecrosis is not completely understood. The most prominent etiological factor is the effect of radiation on the endothelial linings of the vessels resulting in hypocellularity, vasculitis followed by obliterate endarteritis, ischemia, fistula and pathological fracture of

the bone.⁵ Osteoradionecrosis is the result of hypoxic, hypovascular and hypocellular tissue, followed by tissue breakdown leading to a nonhealing wound.¹ Mandibular ORN develops most commonly after local trauma, such as dental extractions, biopsies, related cancer surgery and periodontal procedures, but it may also occur spontaneously.

Store et al⁶ using DNA hybridization demonstrated that bacteria may play a fundamental role in the pathogenesis of ORN; teeth present in the field of irradiation might represent the port of entry for microorganisms. He demonstrated the existence of a diverse microbiota of the medullar parts of the mandible, visualized by scanning and transmission electron microscopy and by DNA-DNA hybridization in a checkerboard assay. Based on analysis of irradiated bone biopsies from a high number of patients with postoperative complications, Hansen et al also demonstrated an association between actinomyces and infected osteoradionecrosis (ORN).⁷

A new hypothesis proposes that ORN occurs by a radiation-induced fibro-atrophic mechanism, including free radical formation, endothelial dysfunction, inflammation, microvascular thrombosis, fibrosis and remodeling and finally bone and tissue necrosis.⁸ The key event in the progression of ORN is therefore the activation and dysregulation of fibroblastic activity that leads to atrophic tissue within the previously irradiated area.⁹

PREDISPOSING FACTORS

Radiation	
Total dose of radiation and time factors. ¹⁰	Doses of < 67.5 Gy delivered in < 6.5 weeks resulted in no cases of ORN as compared to a 50% incidence with higher doses delivered in < 6.5 weeks
Energy source. ¹¹	Brachytherapy sources deposit a higher dose within a short period of time resulting in a higher risk of ORN. Higher energy photons have a higher exit beam dose, and are more likely to increase the risk of ORN.
Tissue density in radiated volume.	Bone has density 1.6 to 1.8 times greater than soft tissue, absorbing more photons with higher energy deposition. The mandible has a higher density compared to maxilla, which may explain the higher incidence of mandibular involvement.
With recent introduction of new modalities of RT, like intensity modulated radiotherapy (IMRT) that reduces the volume of exposure of maxillary and mandibular bone to high radiation doses, further reduction of ORN is expected. ^{12,13}	
More recent advances in IMRT, helical tomotherapy (HT), which is still under evaluation, could be the next advancement in reducing the radiation doses delivered to nontumoral tissues and other areas by achieving conformal dose distributions. ¹⁴	
Trauma and Surgery	
Trauma	According to Marx, ¹⁵ Trauma may or may not be an initiating factor. When trauma is associated, it is usually caused by tooth removal (88%). Role of trauma is part of comprehensive pathologic process, involving cellular death and collagen lysis, which places a greater energy, oxygen and other metabolic demands on tissues unable to meet them. Furthermore, a study by Bagan et al reported about 50% of spontaneous ORN appearing without history of previous tooth removal. ¹⁶
Surgical procedure	Surgical procedure to jaws after irradiation increases the risk for developing ORN, since vascularization of tissues is impaired. ¹⁷ In addition, factors linked to preirradiation surgery are loss of periosteal blood supply due to a marginal mandibular resection, unstable fixation of the mandibular split osteotomy leading to malunion or nonunion and inadequate tissue coverage of the bone after resection of a tumor. ¹⁸
Habits and Drugs	
Tobacco and alcohol	One of the most prevalent negative factors associated with the ORN patients is the continued heavy use of alcohol and tobacco by 86% of them. ¹⁹ These strong tissue irritants significantly contributes to the breakdown of mucosa and exposure of bone.
Steroids and anticoagulants	Steroid use before or after radiation therapy reduced the risk of ORN by 96%, by preventing progression to thrombosis, atrophy and necrosis, credited to the protective effect related to inhibition to the initial inflammatory phase of ORN. ²⁰ On same lines, anticoagulant therapy use also significantly reduced the ORN risk.

CLINICAL PRESENTATION

Osteoradionecrosis clinically includes pain, swelling, non-resolving painful mucosal ulcer with evidence of exposed bone or sequestrum, trismus, malocclusion, telangiectasia formation, exposed bone in the form of oral cutaneous fistula formation, pathologic fracture in severe cases.¹⁷ Pain and evidence of exposed bone are the chief clinical features of ORN. Initially, the patient may have trismus, fetid breath,

and an elevated temperature, although acute infection usually is not present. Exposed bone with a gray to yellow color is seen in association with intraoral and extraoral fistulae. Pathological fractures may be present in severe cases. The exposed bone often has a rough surface texture that abrades adjacent soft tissue and causes further discomfort. The tissues surrounding the exposed bone may be indurated or ulcerated from infection or recurrent tumor.

On physical examination, missing hair follicles, surface texture changes and color changes are common findings that assist clinicians in assessment of the area of radiation injury.²¹

Histologically, there is evidence of diminution or obliteration of the lumen of the vessels and sclerotic changes in their walls. Bone trabeculae are reduced in width and in number, so that, there is increase in size of some of the marrow spaces, which contain necrotic debris. New bone formation does not occur as a rule, although some observers state that it may develop beneath the periosteum in some cases.²²

Sequestration is slow because not only the osteoblastic but also the osteoclastic mechanism of the bone has been inhibited or destroyed. When it does occur, a large piece of bone is generally separated from the unaffected vital part of the mandible. While this separation progresses, infection may progress to the fascial planes and cause deep cellulitis of the face and neck.²³

MANAGEMENT OF ORN

Before Radiotherapy: Prevention of Osteoradionecrosis

Radiotherapy regimes, such as accelerated fractionation and hyperfractionation, improve local control but at the expense of increased local complications.²⁴ Newer protocols, such as 3D conformational radiation therapy and intensity modulated radiotherapy are able to maximize delivery to treatment areas and minimize dose to surrounding normal tissue.²⁵ Nevertheless, preventive measures should be practiced to reduce the incidence and severity of ORN.

Preventive measures prior to radiotherapy: Along with complete dental evaluation, radiographs of all the teeth as well as the jaws are needed to be checked for unerupted

teeth and any bony pathology. Caries and periodontal evaluation with individual prognosis and a treatment plan should be prepared.

Recent studies have shown no difference in the ORN rates in patients who had extractions prior to or after radiotherapy, however, it is still the policy to remove unrestorable teeth prior to radiotherapy.²⁵⁻²⁷ In regard to this, most authors claim that the prophylactic removal of periodontally involved dentition exposed to high doses of radiation minimizes the ORN risk.²⁸ The patient's motivation and compliance should be taken into account when assessing which teeth can be salvaged and which should be removed. The extractions should be carried out in a nontraumatic manner with minimal damage to the surrounding tissues.

Hygiene during radiotherapy: During radiotherapy, mucositis and xerostomia are commonly seen. Regular mouthwashes and meticulous oral hygiene is essential during this period, since the conditions during xerostomia may lead to dental caries.^{25,29} Patient education regarding meticulous oral hygiene and the need for life-long regular follow-up should be carried out.²⁶ The importance of good oral hygiene utilizing plaque control and fluoride gel applications is critical.

Other measures: Patient medication should be reviewed as bisphosphonates used in various conditions, such as osteoporosis, Paget's disease and metastatic breast disease have been shown to cause osteonecrosis of the jaws. The exact mechanism is not known but is related to suppression of osteoclastic activity.³⁰ Paradoxically, bisphosphonates have also been used in the treatment of osteoradionecrosis, highlighting our incomplete understanding of the condition.³¹

After radiotherapy: The patient should be reviewed regularly to ensure good oral care and look for signs of dental disease or mucosal damage.

CONSERVATIVE MANAGEMENT

Conventional treatment	80 to 90% of early stage diseases are successfully managed with saline irrigation, analgesics, antibiotics, local débridement, sequestrectomy, observation and understanding the long-term time aspects of therapy. ³²
Drugs and vitamins	<i>Pentoxifylline (PTX):</i> Dion et al first reported that 1200 mg/d of PTX administered for six months to 12 patients with 15 sites of radiation induced soft tissue necrosis significantly accelerated healing. ³³ PTX is an antioxidant methylxanthine derivative with an antitumor necrosis factor-alpha effect. <i>Alpha-tocopherol (Vitamin E):</i> Scavenges free radicals generated during oxidative stress and protects cell membranes against lipid peroxidation. Vitamin E also has antioxidant properties. ³⁴ These two drugs act synergistically as potent antifibrotic agents. ⁸
Ultrasound therapy	Ultrasound therapy using 1 watt/cm ² ; 3 MHz pulse, 1:4; 15 minutes a day for 60 days combined with metronidazole and local débridement induces neovascularity and cellularity in the irradiated volume. ³⁵

Beumer et al³⁶ showed healing in all cases of spontaneous ORN, treated conservatively. Peters et al³⁷ reported healing in all 11 cases of idiopathic ORN treated with either gentle or spontaneous removal of loose sequestra. More recently, Wong et al³⁸ managed to avoid surgery or hyperbaric oxygen (HBO) therapy in 20 of 32 cases treated conservatively, although mean time for healing was 100 weeks. To conclude, the role of infection in ORN, however, is still unclear even if recent reports have confirmed their importance.³⁹

HYPERBARIC OXYGEN THERAPY (HBO)

HBO therapy is a treatment modality which provides an increased oxygen tension at the tissue level to promote healing, especially in wounds with a compromised vasculature. This is accomplished by placing a patient in a pressure-tolerant chamber, either alone (in a monoplace chamber) or with more than one patient or a therapist (in a multiple chamber). The chamber is pressurized at 2.4 atmospheres absolute, and depending on the protocol, patients remain inside for one hour.⁴⁰

The only controlled randomized study in the literature is that of Marx and others. They compared the use of HBO versus antibiotic coverage in the prevention of ORN, when extractions were performed in patients who had undergone radiation treatment. Both groups had 37 patients in each of them. In the group that received the antibiotic prophylaxis, 11/37 patients developed ORN. In the group of patients who only received HBO dives, only 2/37 patients developed ORN.⁴¹

HBO with surgical débridement resulted in a much higher rate of pain resolution, reconstruction and restoration of function within 18 months compared to HBO and irrigation alone.⁴²

Hyperbaric oxygen alone has resulted in some unacceptable loss of function and poor esthetic outcomes; therefore, it must be combined with surgery for the best outcome.

The adverse effects of HBO therapy can range from mild to severe.⁴³ Commonly seen adverse effect during hyperbaric oxygen treatment is the failure of pressure to equalize on both sides of the eardrum, which results in squeezing of the delicate vessels of the eardrum, resulting in pain and bleeding in the middle ear. Mucous plugs, a further adverse effect, may develop in patients with congested sinuses, asthma, or obstructive airway disease, resulting in extreme pain. In the alveoli of the lungs, rupture may occur resulting in tension pneumothorax or in severe cases, air embolism. These complications can be avoided by careful patient selection. The benefits of hyperbaric

oxygen therapy are great, and despite the possible complications, in many cases its value greatly outweighs the risks associated with the treatment.

More recent papers including a prospective randomized controlled study by Annane et al,⁴⁴ showed no benefit of HBO over placebo. In addition, it is an expensive, scarce, time consuming resource and is not suitable for all patients.^{38,45,46}

SURGICAL RECONSTRUCTION

Advanced disease, including pathological fractures requires aggressive surgical management. The development of myocutaneous flaps and the use of microvascular free bone flaps, as part of reconstruction surgery, allowed substantial modifications in the decision making process of the extent of the surgical ablation of extensive ORN.³⁴

Well-vascularized fascia and overlying subcutaneous tissue can be used to fill dead spaces and cover bony segments with the use of fixation plates. This reduces postoperative infection, promotes primary wound healing and improves esthetic appearance.⁴⁷ Radical resection with free microvascular reconstruction using a free fibular graft offers significant advantages, especially in advanced cases.^{11,48}

CONCLUSION

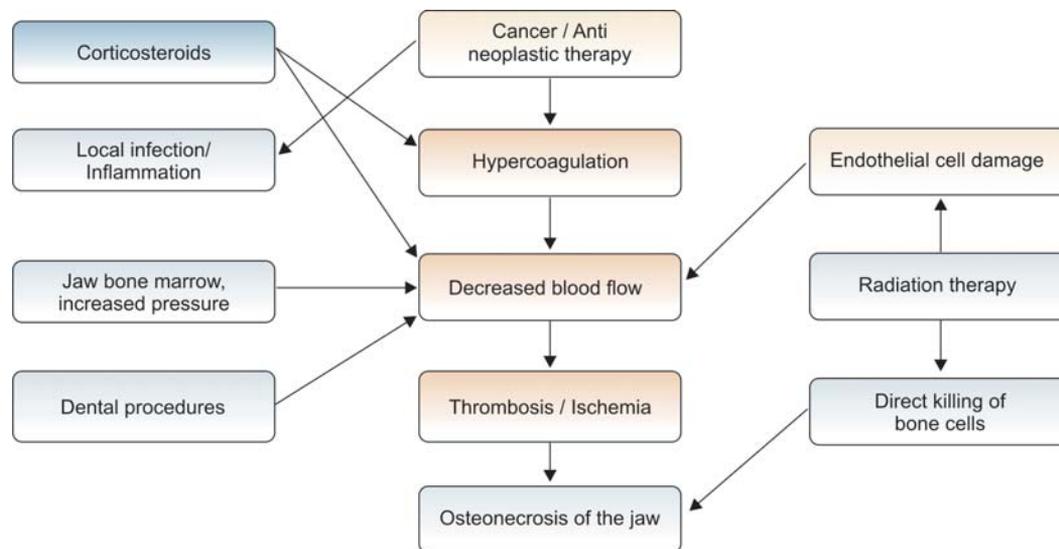
Head and neck cancer patients continue to pose a challenge for surgeons and oncologists.

Prevention of ORN by regular follow-up and early diagnosis should be the goal of every health care professional managing patients with head and neck cancer.

Improved radiotherapy protocols, multidisciplinary preventive care and reconstructive surgery can help to improve the quality of life of patients suffering from ORN.

Recent advances like free tissue surgical transfer, should be considered as treatment of choice for long established cases of ORN, particularly with pathological fracture.

Flow Chart 1: Potential mechanisms for development of osteonecrosis of the jaw
 Courtesy: Journal of oncology practice 2006;2(1):7-14.



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