Osteoradionecrosis of the mandible: Etiology, prevention, diagnosis and treatment

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ABSTRACT

The treatment of head and neck cancer remains a challenge. Despite advances in surgical reconstructive techniques, most patients will require adjuvant therapy in the form of radiotherapy or chemo-radiotherapy to improve locoregional control.

The short- and long term side effects of radiotherapy can be difficult to treat. In this review the causative effects and pathogenesis of osteoradionecrosis of the mandible will be highlighted. In addition, preventive measures and clinical features of radiotherapy induced damage will be presented. Finally, medical and surgical management of osteoradionecrosis, as well as, reconstructive surgery of the mandible will be discussed. At the end of this paper the reader should have up to date knowledge concerning the etiology, prevention, diagnosis and treatment of patients with osteoradionecrosis of the mandible.

KEY WORDS

Fibula free flap, head and neck cancer, hyperbaric oxygen therapy, mandibula, microsurgery, osteoradionecrosis, radiotherapy oral hygiene

INTRODUCTION

The treatment of head and neck cancer remains a challenge. Despite advances in surgical reconstructive techniques, about two thirds of patients will require adjuvant therapy in the form of radiotherapy or chemo-radiotherapy to improve locoregional control.\(^{[1-3]}\)

The initial effects of radiotherapy to the oral tissues such as mucositis and loss of taste are troublesome but short lived resolving within a few weeks. Xerostomia may be more persistent but can be managed with supportive therapy such as sialogues and artificial saliva.\(^{[4]}\) Osteoradionecrosis is the long term and most serious side effect of radiotherapy. The definition of osteoradionecrosis is generally accepted as presence of exposed bone in an irradiated field, which fails to heal within a three-month period.\(^{[5]}\) Early presentation, within 2 years, is thought to be related to high doses of radiotherapy (> 70 gray) whereas late presentation is usually secondary to trauma and delayed wound healing within compromised tissue.\(^{[6]}\) The cause of osteoradionecrosis is multifactorial and the aim of this paper is to describe causative factors, pathogenesis, preventive measures and treatment options for osteoradionecrosis of the mandible.

CAUSATIVE FACTORS OF OSTEORADIONECROSIS

The incidence of osteoradionecrosis varies widely in the literature ranging from 1% to 37%\(^{[4]}\). The most representative study, however, with a retrospective review of 830 patients showed an incidence of 8.2%\(^{[6]}\). The cause of osteoradionecrosis is radiation induced tissue damage. This damage is compounded by the fact that...
the mandible is essentially an end-artery system supplied by the inferior alveolar artery, with minor supply from the bony attachments. With ageing and atherosclerotic changes there is increased dependence on blood supply from the attachments. In addition, both the mandible and maxilla are unique in being the only bones in the body that are exposed directly to the external environment through the gingival attachment of the teeth. Any breaches in the integrity of the tissues result in healing with an increase in bone turnover. In an irradiated field, minor insult such as periodontal disease, pulpal infections and procedures such as dental extractions can result in delayed healing and in some cases develop into osteoradionecrosis. Only a minority of patients goes on to develop osteoradionecrosis following radiotherapy and this number is thought to be falling. This, in part, is due to our better understanding of the etiology of the condition and a multidisciplinary approach. Other factors include developments in radiotherapy and radiotherapy protocols, better patient education and institution of more preventative measures. It is important to remember that head and neck cancer patients are elderly, may have co-morbidity such as diabetes or hypertension, are from a poorer socio-economic class and tend to be smokers and alcohol consumers. A significant proportion will continue to smoke and drink following diagnosis and treatment.

Radiation dose: It has been shown that increasing the external beam radiation dose above 50 Gray gives a significantly increased risk for developing osteoradionecrosis.[6]

Time to deliver the radiation dose: Radiotherapy gives a progressive injury to tissues at a cellular and subsequently humoral level. If the entire dose is given in a short period of time, this will prevent the remaining viable local non-tumor cells from recovering and therefore will cause more damage. In the same fashion different schemes of fractionated delivery of irradiation have been shown to reduce the complications of radiotherapy.[7-9]

Mode of delivery, location and volume of irradiated tissue: More localized delivery by means of e.g., brachytherapy limits radiation damage to surrounding tissues compared to external beam irradiation where an entire block of tissue is irradiated. Less vascularized parts of the mandible such as the posterior part or surgically manipulated parts are more susceptible to osteoradionecrosis. Furthermore, optimal planning and simulation of irradiation fields will help minimize irradiation of surrounding non-involved tissues.

Inadequate oral hygiene: Intraoral tissues are damaged by irradiation, which causes mucositis and xerostomia. These conditions, in combination with poor dental care or a poorly fitting tissue-borne prosthesis, will give rise to odontogenic and periodontal infections. This again can lead to osteoradionecrosis.

Surgery: Any surgical procedure to the jaws that is performed after irradiation will increase the risk for developing osteoradionecrosis since vascularization of these tissues is impaired. In addition, predisposing factors for the development of osteoradionecrosis linked to pre-irradiation surgery have been suggested as well. These factors are loss of periosteal blood supply due to a marginal mandibular resection, unstable fixation of the mandibular split osteotomy leading to mal-union or non-union and inadequate tissue coverage of the bone after resection of a tumour.[10]

PATHOGENESIS OF OSTEORADIONECROSIS

In simplistic terms, radiation produces its deleterious effects through production of free radicals, which result in mitotic cell death. The effects will be greatest on rapidly dividing cells such as the mucosa. Remodeling cells such as fibroblasts, osteoblasts and osteoclasts will show changes when they try to divide, such as during healing.[11] Damage to the microvasculature results in initial hyperemia followed by endarteritis, thrombosis and eventual obliteration. This results in the picture described by Marx as the 3 ‘H’s or Hypocellularity, Hypoxia and Hypovascularity.[5,12]

PREVENTION OF OSTEORADIONECROSIS

Radiotherapy regimes such as accelerated fractionation and hyperfractionation, improve local control but at the expense of increased local complications.[12] Newer protocols such as 3D conformal radiation therapy and intensity modulated radiotherapy are able to maximize delivery to treatment areas and minimize dose to surrounding normal tissue.[13] Nevertheless, preventive measures should be put in place to help to reduce the incidence and severity of osteoradionecrosis. These measures should be applied both before and after the radiotherapy.

Multidisciplinary approach: As soon a head and neck malignancy is diagnosed, the patient should be reviewed...
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within a multidisciplinary team. This team should include a dentist who is sufficiently experienced in dealing with oral cancer patients. If such a person is not available within the team and the patient is likely to receive radiotherapy, then a referral must be sought.

Preventive measures prior to radiotherapy: The patient should have a full dental evaluation. This should include radiographs to show all the teeth as well as the jaws to check for unerupted teeth and any bony pathology. A panoramic radiograph should be a minimum but ideally, periapical views of all the teeth should be taken. All the teeth should be meticulously charted for caries and periodontal pocketing. Each tooth should be given an individual prognosis and a treatment plan completed and discussed with the patient. It is important to educate the patient regarding meticulous oral hygiene and the need for life long regular follow up. The patient’s motivation and compliance should be taken into account when assessing which teeth can be salvaged and which should be removed. All teeth should be cleaned and scaled. The patient should be encouraged to rinse with a fluoride and antibacterial mouth wash on a regular basis and high risk patients should have custom trays made to assist in regular fluoride treatment. Patients with no teeth are easier to treat but should still have a baseline radiographic evaluation to check for buried teeth. Dentures should be inspected for fitting to ensure minimal trauma to the tissues.[13]

The timing of extractions is controversial but 2-3 weeks prior to radiotherapy is advised to ensure timely healing. The extractions should be carried out in a non-traumatic manner with minimal damage to the surrounding tissues. Recent studies have shown no difference in the osteoradionecrosis rates in patients who had extractions prior to radiotherapy or after radiotherapy, however it is still the policy in most institutions to remove unrestorable teeth prior to radiotherapy. Teeth with questionable prognosis should be carefully discussed with the patient.[6,13,14]

Hygiene during radiotherapy: During radiotherapy, the patient will experience mucositis and xerostomia. Regular review with the dentist is essential to minimize discomfort. The xerostomia will cause dryness of the mouth due to lack of saliva, which is essential to wash away debris and dilute the plaque. Regular mouthwashes and meticulous oral hygiene is essential during this period. A dry mouth will sometimes result in patients resorting to foodstuffs that are sloppy and sticky and have more carbohydrate component which together with a low saliva flow rate may lead to increased caries.[4,13]

Other measures: Patient medication should be reviewed as Biphosphonates, 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.[15] Paradoxically, biphosphonates have also been used in the treatment of osteoradionecrosis, highlighting our incomplete understanding of the condition.[16]

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

CLINICAL FEATURES

Tell tale signs of radiotherapy may be present on the skin such as thin skin, pigmenitary changes, lack of hair and telangiectasis. Intraorally, the mucosa may be dry with frothy sputum but these are relatively acute changes following radiotherapy. The patient may have a non-resolving painful mucosal ulcer with evidence of exposed bone or sequestrum [Figure 1]. This is usually in the posterior mandibular region. There may be trismus and this usually appears 3-6 months following radiotherapy. There may be exposed bone seen through the skin, in the form of an orocutaneous fistula [Figure 2] or the patient may present with a pathological fracture [Figure 3].[17]

MEDICAL MANAGEMENT

Medical management of osteoradionecrosis is essentially supportive with pain relief and treatment of infection. If the patient is dentate, preventative measures as outlined above should continue with advice on diet and nutrition as well as oral hygiene. Small wounds may be debrided superficially and any loose necrotic bone removed. Infection tends to be secondary and systemic antibiotics should be reserved for symptomatic cases. Simple panoramic views of the upper and lower jaw will show foci of change [Figure 4] and a computed tomography (CT) scan can be performed to delineate affected areas. A number of authors have advocated conservative management. Beumer et al.,[18] showed
healing in all cases of spontaneous osteoradionecrosis, treated conservatively. Peters et al.,[19] reported healing in all 11 cases of idiopathic osteoradionecrosis treated with either gentle or spontaneous removal of loose sequestra. More recently Wong et al.,[20] managed to avoid surgery or hyperbaric oxygen (HBO) therapy in 20 of 32 cases treated conservatively, although mean time to healing was 100 weeks.

The methyoxanthine derivative, pentoxifylline, used in the treatment of intermittent claudication has been used with some success in radiation induced soft tissue injury but its efficacy in ORN is unclear.[16]

HBO therapy has been shown to be effective, though not universally accepted. In accordance with Marx’s original protocol, this can either be used in the medical management of the patient or in preparation for more radical surgery. In cases presenting early, 30 HBO dives to 2.4 atmospheres for 90 minutes have been advocated. Good responders should continue to a total of 40 dives. Those planned for radical surgery should have 20 dives preoperatively followed by 10 dives post operatively.[21]

There is general agreement that, at least in the short term, HBO therapy raises tissue oxygen levels and causes proliferation of blood vessels, fibroblasts and osteoblasts.[6] Marx's original studies showed that only 2 of 37 patients in the HBO group and 11 of 37 in the penicillin (control) group, developed osteoradionecrosis. However many question the protocols of the original papers and its success has never been replicated.[21]

More recent papers including a prospective randomized controlled study by Annane et al.,[22] showed no benefit of HBO over placebo. In fact the HBO group fared worse and the trial was terminated early. Most institutions have a more selective use for HBO and larger randomized controlled trials are needed. In addition, it is an expensive, scarce, time consuming resource and is not suitable for all patients.[20,23,24]

**Reconstructive surgery**

Goals of reconstruction: Bony reconstruction of the jaws in cancer-related deformities presents several unique problems that have historically produced low success rates and high morbidity.[24] Large spans of discontinuity, soft tissue deficiency, irradiated tissue and extreme scarring with bony displacement are some of the more obvious problems. Particular goals of reconstruction are to restore function of the jaw bone, especially with regard to food processing, swallowing and intelligible speech production and to restore the appearance of the (lower) face.[26]

Hyperbaric oxygen and delayed bone graft reconstruction: Most authors feel that the availability of reconstructive microvascular surgery has made Marx’s algorithm of preoperative HBO followed by resection and delayed nonvascularized bone graft reconstruction[27] outdated and of questionable efficacy.[25] However, if microvascular expertise or instrumentation is not available, it has been stated that this 2-phase bone healing concept can produce predictable reconstructions, although no data proving this were presented.[24] After 30 presurgical HBO treatments, a sequestrectomy is performed in combination with bony stabilization with a reconstruction plate and immediate soft tissue coverage using a myocutaneous flap. Routinely, the pectoralis major myocutaneous flap is used, but latissimus dorsi, trapezius or sternocleidomastoid flaps may also be used to fit a particular need. Postoperatively, each patient receives 10 HBO treatments and about three months later bony reconstruction is performed using a nonvascularized posterior ilium bone graft (cortical bone and cancellous bone marrow).[24]

Surgical management of advanced osteoradionecrosis

Advanced, symptomatic cases, which have failed conservative measures, will require radical surgery.

Preoperative work-up

Exclusion of local recurrence: The first and most important step is to rule out a local recurrence of a malignancy through a biopsy.[25] Unfortunately, a recurrence will not be identified in 21% of cases until pathologic examination of the sequestrectomy specimen has been completed.[14] Therefore, some believe that surgical treatment of osteoradionecrosis should be as radical as primary tumor surgery.

A computed tomography scan or magnetic resonance imaging is performed to preoperatively estimate the margins of bony resection. The definite extent of resection, however, can only be determined intraoperatively with margins that demonstrate healthy, bleeding bone.[25]
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often the only and best option for the treatment of advanced osteoradionecrosis.\cite{8,10,14,25,26} In addition, perioperative adjunctive HBO therapy is often given,\cite{14} although it has not been conclusively proven to be of benefit.\cite{23,26} The key to successful treatment in these advanced osteoradionecrosis cases is adequate and radical sequestrectomy and replacement with healthy vascularized tissue with its pedicle outside the radiation field [Figures 1-4]. Furthermore, it should be realized that osteoradionecrosis affects surrounding soft tissue and is not only a disease of the bone.\cite{14}

Several free flaps such as the scapula bone flap (in combination with either a parascapular skin island or partial latissimus dorsi muscle), iliac crest flap or soft tissue only flaps (rectus abdominis and latissimus dorsi myocutaneous flaps) have been used, but the osteocutaneous fibula free flap is generally considered the workhorse flap.\cite{8,14,26,28} The fibula free flap offers many advantages, especially if the defect involves the anterior mandibular arch. It allows the surgical team: to obtain adequate length of bone up to 25 to 27 cm, to perform the reconstructive procedure while doing the resection, to perform multiple osteotomies without endangering its viability and to obtain a vascular pedicle up to 12 to 15 cm which is important because identification of adequate recipient vessels may be difficult in these patients with a heavily irradiated neck.\cite{28} Furthermore, the donor-site morbidity is generally minimal and compares favourable to the iliac crest flap.\cite{29} Sometimes, after radical osteoradionecrosis resection composite through-and-through defects exist,

![Figure 1](image1.png)

![Figure 3](image3.png)

![Figure 2](image2.png)

![Figure 4 a,b](image4.png)

Reconstruction of the mandible after development of osteoradionecrosis in a 54-year old male after 2 year following squamous cell cancer floor of the mouth and mandible resection followed by osteocutaneous fibula free flap reconstruction of the mandible and 70 Gray of radiotherapy. After resection of the entire osteoradionecrotic bone and poorly perfused local surrounding tissues (Figure 1) the floor of the mouth was restored with the skin island of the osteocutaneous fibula free flap (Figure 3) and the mandible was restored with the fibular bone (Figure 2). The anterior neck was resurfaced with an anterolateral thigh free flap due to severe preoperative scarring of the irradiated neck. At 2 years post-reconstruction the patient remained disease free (Figures 4 a,b) and was able to start with dental rehabilitation.
which require a second free flap for reconstruction of the external skin defect of the lower face or neck.\textsuperscript{30,31} As already mentioned, recipient vessel identification and dissection in a previously operated and irradiated neck can be tedious. It often requires more delicate dissections, sometimes with the aid of a microscope. However, it is better to select vessels outside the irradiated field as the superficial temporal or transverse cervical vessels or to select vessels from the opposite neck.\textsuperscript{26,32} Although the cephalic turnover vein for venous anastomosis and the external carotid artery for arterial anastomosis may be used if no native neck vessels are suitable,\textsuperscript{26} it may sometimes be necessary to resort to interposition vein grafts.

**Postoperative results**

Complications: Surgical management of osteoradionecrosis patients is challenging and complex because previous surgery and irradiation results in obliterated tissue planes and higher risk for wound healing problems, respectively.\textsuperscript{26} In experienced hands partial or total free flap loss which requires a second free flap or regional myocutaneous flap may range from 0% to 15%.\textsuperscript{8,10,23,26} Local wound healing problems resulting in dehiscence, plate exposure or orocutaneous fistula formation may occur in 8% to 43%.\textsuperscript{8,10,23,26} Most of these latter complications, however, can usually be managed successfully with conservative treatment.

Tumor recurrence and survival: Reported tumor recurrence rates after osteoradionecrosis reconstruction range from 0% to as high as 25% with a follow-up time up to 62 months.\textsuperscript{10,26,28} Patient survival rates (not necessarily disease free) usually are around 70% to 80% with a maximum follow-up of 62 months.\textsuperscript{10,26,28}

Functional and aesthetic outcome and dental rehabilitation: Studies on outcome and dental rehabilitation after osteoradionecrosis are limited. Very few patients after osteoradionecrosis reconstruction receive osseointegrated dental implants.\textsuperscript{26,33,34} However, there is limited evidence that implants placed in the reconstructed areas have success and survival rates comparable to those obtained in case of implants placed in native bone.\textsuperscript{34} Cordeiro et al., reported long-term functional and aesthetic results of 133 fibula free flap reconstructions of which only 8 were osteoradionecrosis cases.\textsuperscript{33} A total of 45% of all patients were able to have a normal diet, 45% had to use a soft diet and 5% were on a liquid diet. Speech was normal or near-normal in 63% and aesthetics were good to excellent in 59%. Interestingly, these results were better after reconstruction of hemi mandible defects compared to central defects.\textsuperscript{34} Extensive composite defects after radical osteoradionecrosis resection requiring double free flap reconstruction have a poorer long-term aesthetic and functional outcome with a higher occurrence of speech, eating and oral incontinence problems.\textsuperscript{31}

**CONCLUSION**

Head and neck cancer patients continue to pose a challenge for surgeons and oncologists. Osteoradionecrosis can be a cruel blow to patients and their families who have already had to endure treatment for cancer. Improved radiotherapy protocols, multidisciplinary preventive care and reconstructive surgery can help to improve the quality of their lives.

**REFERENCES**

12. Bensadoun RJ, Magne N, Marcy PY, Demand F. Chemotherapy- and radiotherapy-induced mucositis in head and neck cancer
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