Osteoradionecrosis of the jaws – a current overview – Part 1 Physiopathology and risk and predisposing factors

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ABSTRACT

Purpose The aim of this paper is to explore the current theories about definition, classification, incidence and physiopathology of osteoradionecrosis of the jaws. Moreover, it is discussed the predisposing and risk factors for the development of osteoradionecrosis based on the literature review.

Discussion Osteoradionecrosis is one of the most serious oral complications of head and neck cancer treatment. Osteoradionecrosis is a severe delayed radiation-induced injury, characterized by bone tissue necrosis and failure to heal. Osteoradionecrosis either stabilizes or gradually worsens and is notoriously difficult to manage. The most widely accepted theory to explain its cause until recently was the theory of hypoxia, hypovascularity, and hypocellularity. A new theory for the pathogenesis of osteoradionecrosis was proposed. The clinical presentations of osteoradionecrosis are pain, drainage, and fistulation of the mucosa or skin that is related to exposed bone in an area that has been irradiated. The tumour size and location, radiation dose, local trauma, dental extractions, infection, immune defects and malnutrition can predispose its development.

Conclusions A better understanding of risk factors for the development ORN and of the underlying pathophysiology may improve our ability to prevent this complication and help to improve the prognosis for those being treated for osteoradionecrosis.

KEYWORDS

Osteoradionecrosis; jaw; physiopathology; risk factors

INTRODUCTION

Radiotherapy is largely used for treatment of head and neck cancer, as primary therapy, adjuvant to surgery, in conjunction with concurrent chemotherapy or as palliative treatment for late stage and unresectable head and neck malignancies. Although the radiotherapy can increase cure rates, the irradiated patient is susceptible to secondary effects and a series of potential oro-facial complications. These complications can be divided into early and long-term complications.

Early complications of radiotherapy are very frequent, particularly the oral mucositis. It is by far the most common and distressing complication of malignancy treatment and may have such a significant effect on the quality of life that there is the need to interrupt or curtail the cancer therapy [1, 2].

Long term complications of head and neck radiotherapy include dry mouth (xerostomia), loss of taste, limitation of mouth opening (trismus), progressive periodontal attachment loss, dental caries, microvascular alteration, soft tissue necrosis, and less commonly, but one of the worst, osteoradionecrosis (ORN) [3], this latter being considered is the most devastating complication of radiotherapy in the head and neck area [3-5]. In severe cases even death can occur [6]. Patients suffering from ORN experience a substantial deterioration in their quality of life owing to serious clinical symptoms such as chronic spontaneous pain, dysphagia, and facial deformation [7].

A better understanding of risk factors for the development ORN and of the underlying pathophysiology may improve our ability to prevent this complication and help to improve the prognosis for those being treated for ORN.

Many factors have been considered to predispose to the development of ORN, including the tumour size and location, radiation dose, local trauma, dental extractions, infection, immune defects and malnutrition. Nevertheless, ORN may also sometimes occur spontaneously, unrelated to trauma [8, 9]. Many patients with oral cancer also abuse alcohol and tobacco and are in poor general medical condition [10], which, together with poor nutritional status and lack of oral hygiene, may place these patients at higher risk of ORN. The data of the study of Reuther et al. [11], with 830 head and neck tumours patients evaluated during 30 years, suggested that tumour stage, tumour infiltration of adjacent bone and tooth extractions are the most important predisposing factors for ORN.

In this paper we explore the current theories about definition, classification, incidence and physiopathology of ORN. Moreover, it is discussed the predisposing and risk factors for the development of ORN based on the literature review.

DEFINITION

During the years ORN has received many definitions, and therefore it is sometimes difficult to compare epidemiological studies and treatment efficacy. It has also received many clinical definitions.

Probably the first evidence of ORN related to radiotherapy was reported by Regaud in 1922 [12]. Its pathology was further described by Ewing [13] in 1926, under the name 'radiation osteitis'. Meyer [14] classified ORN as one special type of osteomyelitis. Titterington [15] also related ORN to osteomyelitis, providing one of its first definitions, and used the term 'osteomyelitis of irradiated bone'.

In his classic paper on the pathophysiology of ORN, Marx [16] defined it as 'an area greater than 1 cm of exposed bone in a field of irradiation that had failed to show any evidence of healing for at least 6 months'. He also clarified that in ORN there is no intersticial infection, but only superficial contamination.

ORN is best defined as a slow-healing radiation-induced ischemic necrosis of bone with associated soft tissue necrosis of variable extent (Figures 1 and 2) occurring in the absence of local primary tumor necrosis, recurrence, or metastatic disease [17].

The following points seem to be agreed by the majority of the authors:

1. The affected site should have been previously irradiated;
2. There should be absence of recurrent tumour on the affected site;
3. Mucosal breakdown or failure to heal should occur, resulting in bone exposure (except in cases of bones that lie within thick soft tissue integument's, such as the pelvis or femur, or rarely in cases of a pathological fracture of the mandible after irradiation);
4. The overlying bone should be 'dead', usually due to a hypoxic necrosis;
5. Cellulitis, fistulation, or pathologic fracture need not be present to be considered ORN [17].

Two important questions remain to be clarified, (a) the timing of the bone exposure, and (b) the definition of 'dead' bone. The first question has an obvious variability in the literature. Some authors do not comment on time of exposure [18], others recommend a 2 month period before ORN can be diagnosed [4, 19, 20], or even 3 months [21-23] and 6 months [8, 16]. ORN usually develops during the first 6 to 12 months after radiotherapy; however, the risk remains for life, albeit to a lesser degree [24]. Berger and Symington [25] reported two late presentations, one 45 years after a radium implant, and the other 38 years after external beam treatment.

Precaution should be taken not to have a too short period of waiting, because mucosal radionecrosis can occur without ORN, and over-diagnosis will occur. Furthermore, short periods of exposed bone should also not be used, because any surgery and/or extraction performed usually can take up to 1 month to heal. On the other hand, long periods such as 6 months are difficult to establish at clinical practice, and some intervention before this time is certainly needed. Therefore we propose that in the definition of ORN, the bone exposure should be of at least 3 months.

The second question, related to the definition of what is 'dead' bone is more difficult to answer. Although the majority of the authors agree that for a correct diagnosis of ORN, the underlying exposed bone should be necrotic, how to determine this? With a short period of observation, simple radionecrosis of the mucosa with no underlying necrotic bone can be mistaken for ORN [26]. If surgery is performed in the area, bleeding bone can give a helpful guide to the necrotic limits; however it would be of advantage if the diagnosis could be performed none invasively. Therefore, the need of more objective and adequate investigative tools is

crucial, since it would help equally in the definition, diagnosis, classification of severity, and of course, the outcome of the different treatments.

INCIDENCE

The incidence of ORN has a great variability in the literature, and the absolute incidence and prevalence of ORN of the jaws after radiation therapy for treatment of head and neck cancer are unknown [24]. Clinical evidence of ORN related to radiotherapy was first reported by Regaud [12]. Reviewing studies from the literature, most of which are retrospective, one finds an overall incidence of ORN of 10.31% before 1968, and of 6.28% after that [27]. The year 1968 was arbitrary chosen by Clayman [24], because at this time almost all radiation oncology units had embraced megavoltage therapy, and we have used it as well, updating all the published incidence studies of ORN. In the biggest investigation ever made, of Reuther et al. [11], a large study population of 830 patients over a period of 30 years was evaluated regarding the occurrence of osteonecrosis and its associated predisposing factors. The incidence of ORN was 8.2%.

Some conclusions can be derived about these facts: (1) not many clinicians reliably report complications such as ORN, and therefore an under reporting may occur; (2) the definition and diagnosis of ORN is very variable. It is therefore very likely that ORN has been over-diagnosed, because many studies considered ORN only as an area of exposed bone, not taking in consideration the time of exposure or the status of the underlying bone; (3) the follow-up period to identify ORN was not the same in the literature, and should be extended for up to 7-8 years, because ORN can occur many years after radiotherapy; therefore, under diagnosis can occur; and (4) the majority of the studies have been retrospective, which by its one has many disadvantages. The few prospective studies published have however very short follow-up times, which is understandable, but there should be more effort in conducting long term prospective studies.

Its incidence is three times higher in dentate than in edentulous patients, mainly as a result of injury from extractions and infection from periodontal disease [21, 28-30].

LOCATION

The higher susceptibility of the mandible has been reported to be attributable to its lower blood supply compared with the maxilla. The compact bone structure of the mandibular bone has also been suggested as a reason for ORN susceptibility [23, 31].

It has been discussed whether the primary tumor site may influence the onset of ORN [9, 30-33]. In the study of Curi and Dib [34], a positive correlation was identified between tumor site and ORN incidence. Oral cancers (82 cases, 78.8%) showed the highest incidence of ORN, especially those of the tongue, retromolar region, and floor of the mouth. In theirs opinion, possible reasons for the higher incidence of ORN at these oral sites are the direct involvement of the mandibular bone in the radiation fields and the aggressive and radical surgical approach necessary for tumor resection. These surgical procedures often consist of mandibular osteotomies or mandibulectomies that are traumatic to bone tissue. Other head and neck cancer sites did not need osteotomy or mandibulectomy for tumor resection, and therefore there were fewer traumas to bone tissue. The aggressive surgery necessary for oral cancer resection frequently involved removal of arteries necessary for the

maintenance of mandibular blood flow, possibly increasing the risk of ORN [35]. Other authors agree about a positive relation between ORN and tumor primary site [30, 32].

CLASSIFICATION

Many authors have attempted a classification of ORN, and the majority has relied on the history and clinical progression of the disease, or its response to treatment.

Daly et al. [36] staged bone necrosis, but omitted to mention how they classified these stages. Coffin [37], in 1983 examined 2,853 cases of patients who had radiotherapy for head and neck malignancies. He suggests that ORN develops in two forms: (a) minor, and (b) major. The minor form was considered to be a series of small sequestra which separate spontaneously after varying periods of weeks or months. These small areas can be seen clinically but cannot be demonstrated radiologically. The major form was defined when necrosis occurs of such an extent as to involve the entire thickness of the jaw, and a pathological fracture is inevitable. This form can obviously be seen radiologically, and is extremely rare in the maxilla (only 1 case in this series).

Morton and Simpson [38] in 1986 subdivided ORN into ‘minor’, ‘moderate’ and ‘major’ groups. Minor ORN consisted of ulceration with exposed bone and a history of bony spicules which healed spontaneously over a period of months. Moderate cases consisted of exposed bone and small sequestra limited in nature and healing spontaneously with conservative treatment within 6 to 12 months. Major ORN consisted of large areas of exposed bone, with formation of large sequestra, possible fracture and sinus formation. These cases often progressed rapidly, lasting in excess of one year and often requiring radical treatment.

Clayman [24] used a classification of ORN related to the overlying mucosa being intact or not. He uses the term Type I for the cases in which bone lysis occurs under intact gingiva or mucosa, and Type II, a more aggressive type, called ‘radiation osteomyelitis’, when the soft tissues break down, exposing the bone to saliva, occurring secondary contamination. He suggest that type I cases heal with conservative therapy, and the type II does not.

There is obviously a necessity for a more objective/quantitative classification of ORN, and probably the only way to obtain it is by the use of more adequate investigative tools. According to Hutchinson [4], this investigative tool should be able to offer the following: (1) record quantitatively and qualitatively the severity and extent; (2) monitor progress of treatment; (3) predict patients at risk; (4) predict risk factors more confidentially; (5) permit comparison of treatment regimens; (6) predict the bone level damage above which surgery is essential.

PHYSIOPATHOLOGY

The understanding of the pathophysiology of ORN has been a controversial subject since its first appearance in the early 1920’s. Many theories of how it occurs have been formulated.

Early experimental models of the pathophysiology of ORN showed evidence of bacteria in tissues affected by ORN, and documented microscopic tissue changes, namely thickening of arterial and arteriolar walls, loss of osteocytes and osteoblasts, and the filling of bony cavities with inflammatory cells [39]. This gained

popularity when Meyer proposed his radiation, trauma and infection theory [14]. He suggested that injury provided the opening for invasion of oral microbiological flora into the underlying irradiated bone. Other authors agreed and referred to ORN as secondary infection after injury to devitalised bone, and even as radiation-induced osteomyelitis [15]. Meyer's theory lasted for a decade and became the foundation for the popular use of antibiotics with surgery to treat ORN.

Marx [8] examined the traditional concept of the pathophysiology of ORN described by Meyer [14], questioning the occurrence of ORN cases without trauma or infection. To test his hypothesis, he studied 26 consecutive cases of ORN from which 12 en bloc resection specimens were cultured and stained for micro-organisms (aerobes, anaerobes and fungi). He cultured and stained also osteomyelitis specimens of the mandible, maxilla and long bones, and infected grafts of the jaws and long bones. The microbiology results showed that all specimens where infected superficially but no organisms could be cultured or observed in the deep, so called "infected bone" of ORN. The micro-organisms identified on the surface varied greatly, suggesting saprophytic contaminants (streptococci, *Candida* species, and Gram negative organisms). In contrast, osteomyelitis and infected bone grafts to long bones consisted primarily of one pathogen, usually a staphylococcal species. Osteomyelitis and infected bone grafts of the jaws showed a more varied group of organisms, including *Bacteroides* and *Eikenella* species as well as *Staphylococcus aureus*, which were not encountered on the surface of ORN bone. He concludes that micro-organisms play a minor role in the pathophysiology of ORN of the jaws, as well as trauma.

The histological findings noted by Marx [8] showed endothelial death, hyalinisation and thrombosis of vessels with a fibrotic periosteum. Bone osteoblasts and osteocytes were deficient, with fibrosis of the marrow spaces. Mucosa and skin also become fibrotic, with markedly diminished cellularity and vascularity of the connective tissue. The overall result was a composite tissue, which is hypovascular and hypocellular, and was proven to be hypoxic compared with non-irradiated tissue by direct measurement [40]. Figure 3 shows some histological aspects of non-viable bone in osteoradionecrosis of the mandible, as demonstrated by lack of nucleoli in bone lacunae (L) and necrosis of bone marrow (NB).

The sequence suggested by this study of Marx [8] is as follows: (a) Radiation; (b) Formation of hypoxic-hypocellular-hypovascular tissue; (c) Tissue breakdown (cell death and collagen lysis exceed synthesis and cell replication), and predispose to a (d) chronic non-healing wound (a wound in which metabolic demands exceed supply). These explanations formed the cornerstone for the use of hyperbaric oxygen (HBO) in the treatment of ORN.

The therapeutic value of HBO was originally observed in controlled in vivo experiments on burns in which daily increases in the oxygen tensions in hypoxic tissues were found to encourage capillary angiogenesis, proliferation of fibroblasts, and synthesis of collagen [41]. Furthermore, HBO can also be bactericidal or bacteriostatic to many pathogens [42]. Mainous et al. [43] were probably the first to suggest the use of HBO for the management of ORN.

Recent papers are convinced that cellular radiogenic effects in bone occur earlier than the well-known vascular alterations [44]. This hypothesis challenges the well-accepted "three-H concept" (hypoxia, hypocellularity, hypovascularity) of Marx [8].

In 2004, Assael [44] hypothesized that ORN occurs by the same mechanism as other types of osteonecrosis (eg, bisphosphonate-related osteonecrosis) and results from decreased osteoclastic bone resorption.

Increased subperiosteal bone deposition in ORN specimens and thickening of the jaw in radiated zones support this theory. Without osteoclasts to resorb the nonviable, radiated bone, healing is impaired [45]. However, there is contradictory evidence to suggest that bisphosphonates may promote healing in patients with ORN [46]. In a 2005 study, using DNA hybridization, investigators showed that bacteria may in fact play a fundamental role in the pathogenesis of ORN, supporting Meyer's original hypothesis [47].

A current theory proposes that ORN occurs by a radiation-induced fibroatrophic mechanism including free-radical formation, endothelial dysfunction, inflammation, microvascular thrombosis, fibrosis and remodeling, and finally bone and tissue necrosis [48]. Three distinct phases are seen [49]: the initial prefibrotic phase in which changes in endothelial cells predominate, together with the acute inflammatory response; the constitutive organized phase in which abnormal fibroblastic activity predominates, and there is disorganisation of the extracellular matrix; and the late fibroatrophic phase, when attempted tissue remodelling occurs with the formation of fragile healed tissues that carry a serious inherent risk of late reactivated inflammation in the event of local injury. Interestingly, Marx had reached similar conclusions, but thought that the driving force of the sequence of events was persistent tissue hypoxia [26].

The theory of radiation-induced fibrosis suggests that the key event in the progression of ORN is the activation and dysregulation of fibroblastic activity that leads to atrophic tissue within a previously irradiated area. After radiotherapy the endothelial cells are injured, both from direct damage by radiation and from indirect damage by radiationgenerated reactive oxygen species or free radicals. Injured endothelial cells produce chemotactic cytokines that trigger an acute inflammatory response and then generate a further release of reactive oxygen species from polymorphs and other phagocytes [50]. The destruction of endothelial cells, coupled with vascular thrombosis, lead to necrosis of microvessels, local ischaemia, and tissue loss. Loss of the natural endothelial cell barrier allows seepage of various cytokines that cause fibroblasts to become myofibroblasts.

The reactive oxygen species-mediated release of cytokines such as tumour necrosis factor α (TNF- α), platelet-derived growth factor, fibroblast growth factor β, interleukins 1, 4, and 6, transforming growth factor β1 (TGF- β1), and connective tissue growth factor, result in unregulated fibroblastic activation and the myofibroblast phenotype persists [50]. These myofibroblasts are characterised by unusually high rates of proliferation, secretion of abnormal products of the extracellular matrix, and a reduced ability to degrade such components.

The imbalance between synthesis and degradation in irradiated tissue is particularly dramatic in bone. The combination of death of osteoblasts after irradiation, failure of osteoblasts to repopulate, and excessive proliferation of myofibroblasts, results in a reduction in bony matrix and its replacement with fibrous tissues. Microradiographic analysis of bone in ORN suggests four possible mechanisms of bony destruction: progressive resorption of osteoclasts mediated by macrophages that are unaccompanied by osteogenesis; periosteocytic lysis, pathognomic of ORN; extensive demineralisation that is secondary to external stimuli such as saliva and bacterial products; and accelerated aging of bone [51]. Ultimately, the myofibroblasts undergo apoptosis and, even decades after radiotherapy, the bone remains paucicellular, poorly vascularised, and fibrosed [52].

THE ROLE OF OSTEOCLAST/OSTEOBLAST ACTIVITY

In normal healthy adult bone, most cells are in the resting phase of the mitotic cycle. However, there is slow but constant cell turnover accompanied by remodelling of the bone structure. Osteoclasts proliferate, resorb bone and disappear, and the osteoblasts proliferate to reconstruct the bone. This process continues throughout life. Trauma stimulates proliferation of osteoblasts mainly from the periosteum to repair the damage to the bone.

Radiation of bone leads to endarteritis obliterans with thrombosis of small blood vessels, fibrosis of the periosteum and mucosa, and damage to osteocytes, osteoblasts and fibroblasts. The damaged osteocytes and osteoblasts may survive until they attempt to divide, when mitotic death occurs. An individual bone cell may undergoe mitotic death at an interval of months or years after irradiation, or it may never divide unless stimulated by trauma. There is therefore a slow loss of bone cells after radiotherapy with a consequent slowing down of the remodelling process, which leads to the risk of bone necrosis [53].

Harris [22] emphasised that the principal problem for the surgeon treating osteoradionecrotic bone is the absence of separation, i.e. sequestration of the nonvital from vital bone, which points to an osteoclast defect. Osteoclasts arise from haematopoietic tissues, followed by vascular dissemination and the generation of resting pre-osteoclasts and osteoclasts in bone itself [54]. Radiation damage to the marrow and blood vessels would explain their absence. Equally important is the absence of the osteoblast which is regarded as the major influence in recruiting and activating the osteoclast. A third consideration was the likelihood that osteoclasts do not find irradiated necrotic bone a suitable substrate for phagocytosis. Jones et al. [55] excluded this possibility showing the production of active resorption pits by cultured osteoclasts on the surface of osteoradionecrotic bone in vitro.

Dambrain [50], using microradiographic analysis of fragments removed from patients with ORN, showed two types of bone resorption. An osteoclastic one not followed by relevant osteogenesis, and another, pathognomonic of post-radiation complications, linked with an altered activity of the osteocytes. These cells are responsible for an irreversible widening of the osteoplasts, set in the poorly vascularized bone regions, in particular in the wall of haversian canals. The coalescence of widened osteoplasts causes polycylic cavities which are a typical feature of ORN.

DIAGNOSIS OF OSTEORADIONECROSIS

The diagnosis of ORN is based primarily upon clinical signs of ulceration of the mucous membrane with exposure of necrotic bone (Figures 1 and 2). Figure 4 shows an initial breakdown of the buccal mucosa. The figures 5, 6, and 7 show the incipient breakdown of the facial skin. The lesion may be accompanied by symptoms of pain, dysesthesia, fetor oris, dysguesia, and food impaction in the area [9, 56]. Early ORN may be asymptomatic [26] even though the its main features of exposed devitalised bone through ulcerated mucosa or skin (Figures 8 and 9) can be seen clearly.

Marx and Johnson [6] found the following physical diagnostic signs to correlate with increased degrees of radiation tissue injuries: (1) Induration of tissue; (2) Mucosal radiation telangiectasias; (3) Loss of facial hair growth; (4) Cutaneous atrophy; (5) Cutaneous flaking and keratinisation; (6) Profoundness of xerostomia; (7) Profoundness of taste loss.

INVESTIGATION OF OSTEORADIONECROSIS

ORN can be investigated by many techniques, including radiographs, CT scans, MRI, doppler ultrasound, nuclear medicine and near infrared spectroscopy. The ideal investigative tool, according to Hutchinson [4] should be able to offer the following: (1) record quantitatively and qualitatively the severity and extent; (2) monitor progress of treatment; (3) predict patients at risk; (4) predict risk factors more confidently; (5) permit comparison of treatment regimens; (6) predict the bone level damage above which surgery is essential.

Regaud noted the absence of a clear line of demarcation between devitalised and vital bone [12]. Attempts to clarify this ambiguity have led to calls for ORN to be defined by radiological evidence of bony necrosis within the radiation field [57], or through histological examination of necrotic bone at the time of eventual resection [11].

Radiographic images are the most commonly used, and the radiological appearance of ORN is that of a mixed radio-opaque radiolucent lesion, with the radiolucent areas representing bone destruction (Figure 10). The cheapest and most readily available image is the orthopantomogram (OPG), which can be supplemented with other extraoral or intraoral radiographs. However they require a substantial alteration in mineral content and extensive involvement of the bone, which only occurs in later stages [58]. Ardran [59] noted that 30% of bone mineral content must be lost before any radiographic change can be seen. Therefore, plain radiographs always underestimate the extent of radiation-damaged bone, and do not correlate with the clinical status of patients [18].

Computer tomography (CT) scans have similar limitations as traditional radiographs for the mandible or maxilla, but can be helpful in temporal bone ORN [4]. Magnetic resonance images (MRI) also have been used, and suggest that fibrosis of bone marrow occurs in ORN [60]. Positron emission tomography (PET) has been advocated as being able to differentiate between ORN and recurrent tumour [61]. Figure 11 shows CT axial sections of a patient with osteoradionecrosis in the mandibular symphysis: with small sequestra of bone (a) and a pathological fracture (b).

Radionuclide bone scanning with technetium methylene diphosphonate (99mTc-MDP) can identify pathophysiologic changes in bone earlier than conventional radiography because scan changes reflect osteoblastic activity and good blood flow [62]. Technetium bone scans have also been used to monitor improvements in tissue viability, before, during and after radiotherapy. Gallium-67 citrate (GA-67) will localise in bone, liver and large bowel. In addition, it will localise in tumours and inflammatory lesions [63]. Gallium scans have been used in ORN, with variable findings, consistent with the fact that ORN is not necessarily associated with inflammation within bone. Thus, gallium uptake may not be of diagnostic value for ORN. However, gallium scans did correlate with clinical findings following treatment, suggesting that persisting positive gallium scans may indicate the need for surgery following conservative treatment [18].

Near infrared spectroscopy (NIRS) is a recognised non invasive method, used largely to monitor cerebral tissue oxygenation and ischaemic changes in neonates [64]. It has been used as an investigation method for ORN in retrospective studies, and shows a reduction of the amount of deoxygenated haemoglobin at sites of ORN, confirming that it is a hypovascular, hypoxic tissue with decreased metabolic rate subtracting little oxygen from haemoglobin [20].

RISK AND PREDISPOSING FACTORS

A review of the available literature implicates the following candidate variables for development of ORN: total radiation dose, photon energy, brachytherapy, field size, fractionation, periodontitis, preirradiation bone surgery, poor oral hygiene, alcohol and tobacco use, dental extractions, tumor size, location, and stage, proximity of tumor to bone, lack of HBO therapy, increased time since radiation, lack of radiation shields, and edentulousness [10, 11, 23, 41].

A) RADIATION FACTORS

The risk of ORN becomes higher as the radiation dose increases [6, 23, 29, 65, 66]. There is universal agreement that high total doses, short regimens using high doses per fraction, large field sizes, and the delivery of radiotherapy through a single homolateral field are all associated with an increased risk of ORN [4]. Gowgiel [39] in his experiences with monkeys showed a direct relation between time of necrosis and the dosage of irradiation (he used 4500 to 11000 rad). The necrosis always started in the interdental papilla of the mandibular molar in the centre of irradiation.

Since the introduction of higher-energy radiotherapy in the mid to late 1960's, the incidence of ORN has fallen from 10.31% to 6.28% [27]. Meyer [14] noted that 5% of his patients treated with orthovoltage developed ORN whereas only 1% to 1.5% developed it with the use of supravoltage (cobalt 60).

Although intersticial therapy is safer than external beam when tumours are situated away from bone, it is associated with an exceedingly high incidence of ORN when used in tumours immediately adjacent to bone. The use of fast neutrons is now known to cause very high rates of particularly severe ORN and soft tissue necrosis, which is almost impossible to manage medically [67].

ORN is unlikely to occur if the radiation dose is below 60 Gy delivered by standard fractions, though total prescribed radiation doses did not give an absolutely clear indication of future clinical course [17]. Other studies report higher incidence of ORN in patients receiving doses higher than 65-75 Gy [23, 32, 56, 68-71]. In the study of Goldwaser et al. [71], patients receiving a radiation dose above 66 Gy increased risk of developing ORN by almost 11-fold. However, because some ORN patients received doses significantly lower than 66 Gy and most non-ORN patients received doses of 66 Gy or higher, it seems clear that dose by itself does not predict absolute risk.

The incidence of ORN is thought to be less common after hyperfractionated radiotherapy at 72–80 Gy, or moderately accelerated fractionated radiotherapy together with a boost of 64–72 Gy [26]. Recent reports have suggested that when chemotherapy is added to radiotherapy the incidence of ORN may be increased [72] whereas the use of intensity-modulated radiotherapy may reduce it [73].

However, Kluth et al. [10] could not establish a correlation between radiation dose and incidence of ORN. They compared a control group to an ORN group, observing a higher total dose in the control group. Fifty percent of the ORN patients actually received a total dose of 60 Gy or less.

Rarely it is seen ORN with doses below 5000 cGy (total dosage) [34, 74]. Cases of ORN usually develop in patients irradiated with doses over 6400 cGy [5, 23].

The use of CHART (Continuous hyperfractionated accelerated radiotherapy) is a relatively new introduction in the radiotherapy field, being applied as a multicentre prospective randomised trial since 1990.

With the low dose per fraction of this regime, there has been a significantly reduced incidence of post-radiation change in normal tissues [75].

Many other precautions related to the radiotherapy itself can be used to minimise the risk of ORN, including multiple fields, reduced total radiation dose, smaller fraction size, devices to move the mandible or maxilla out of the radiation field and radiation shields [58].

Patients who receive high doses of radiation therapy should be submitted to dental extractions of all unrestorable teeth before radiotherapy [5, 23]. Analysis of the field of radiation avoids unnecessary procedures, as extractions performed outside the area of radiation do not constitute a risk factor to the development of ORN [3]. Extractions of unrestorable, but asymptomatic teeth in pre-radiation visits or in the post-radiation period in patients with advanced or end-stage diseases, are not advocated [76].

Reuther et al. [11] found that the time interval until the osteonecrosis occurred was significantly longer for patients with radiotherapy after surgery than for patients with radiotherapy prior to surgery (P=0.002). This may be due to a radiation-induced disturbance of wound healing in pre-surgically irradiated patients.

Sader et al. [77] demonstrate a positive correlation between the incidence of the osteonecrosis and the therapeutic intensity. They observe the complication most commonly in patients treated with combined radio-/chemotherapy before surgery. In the study of Reuther et al. [11] the time interval until the complication occurred was significantly shorter for patients with combined therapy than for those with radiotherapy alone. Chemotherapy is likely to weaken the local immune response by damaging the cellular immune system.

B) TRAUMA

Trauma has been recognised for many years as a predisposing factor to ORN. It was even considered as been part of the pathophysiology of ORN itself, as in the theory of radiation, trauma, infection [14, 78]. Nowadays it is not considered to have a crucial role in its pathophysiology [16] since ORN can occur spontaneously.

However, it is undoubtedly one of the most important risk factors to the development of ORN. Trauma can be delivered to the tissues adjacent to the mandible in several ways, as local trauma due to dentures or others, and surgically, due to teeth extractions and major surgery related to the treatment of the malignancy itself.

Teeth extraction

Unrepairable teeth due to caries, periodontal disease or root lesions can cause infection of the bone and progression to ORN because of low vascular patency and the inability of the mechanisms of repair in irradiated tissues [70]. The irradiated patients present alterations in the salivary glands and in the dental structure, which predispose to progressive periodontal attachment loss, rampant caries and fungal and bacterial infections. These patients can also present fibrosis, resulting in trismus and consequently difficulties in adequate oral care [79].

Several authors consider removal of diseased teeth, especially in the postirradiation period, a main risk factor in the development of ORN [5, 6, 23, 29, 33, 58, 66], but few studies have shown increased risk for ORN development when exodontias were executed before radiation treatment [3] and others show similar results when dental extractions were compared before and after radiotherapy [11, 58].

The pretreatment assessment and dental management of patients receiving head and neck radiotherapy is discussed in detail later in this article.

Resection surgery

Any surgery that has been, or will be, performed within a radiated field increases the risk of developing ORN. Such predisposing factors related to the initial resection include: 1) loss of periosteal blood supply, such as that seen following a marginal resection; 2) inadequate tissue coverage of a defect following extirpation of a primary or recurrent lesion; or 3) improper fixation of an access osteotomy resulting in a nonunion. Celik et al. [80] found in their retrospective analysis that patients who underwent mandibular osteotomy for access (mandibulotomy) and marginal mandibulectomy developed ORN earlier than patients who had a segmental mandibulectomy. This is most likely related to the fact that their segmental mandibulectomy patients underwent immediate reconstruction with free tissue transfer, hence improving the vascularity of the surgical site. The findings of the study of Reuther et al. [11] demonstrated that the more radical the resection of the mandible during surgical therapy of the tumour was, the sooner ORN occurred.

Local trauma

Dentures may cause mucosal irritation and ulceration leading to ORN [36]. After tooth extraction, at least 9 months should elapse for bone remodelling before new dentures are fitted [19]. Jansma et al. [1, 2] recommend that during radiotherapy, the patient should only wear dentures for meals.

C) CARIOUS AND PERIODONTALLY COMPROMISED TEETH

There is a well established association between carious and periodontally compromised teeth and ORN [81, 82]. Radiotherapy directly affects the supporting structures of the teeth, the gingiva, periodontal ligament and bone [83]. The fibres of the periodontal ligament, anchoring the tooth to its adjacent alveolar bone, become hyalinized and irregular, losing their spatial organisation. There is a reduction in blood vessel internal diameter and number, as well as hypocellularity, including osteoblasts and cementoblasts [84]. These effects are added to increase plaque, toxins from the microorganisms contained therein, leading to the development of chronic periodontal disease with continuous destruction of bone and teeth supporting structures [85]. Galler et al. [85] reported three cases of ORN which developed from periodontal disease activity, but the incidence could be much higher.

Murray et al. [28, 29] showed a positive association between dental disease present before radiation therapy and subsequent necrosis of the mandible ($p=0.09$), leading to a recommendation that significant disease be eradicated before irradiation of oral tissues. Unless careful attention is given by the patient to the elimination of plaque with correct tooth brushing technique, this chronic disease will not only cause tooth loss but also cause some of the ‘spontaneous’ ORN cases.

Spontaneous osteoradionecrosis

Although ORN is traditionally associated with trauma, it has been observed to occur spontaneously. In the 1970’s and 1980’s the role of trauma as initiating factor of ORN started to be questioned, since many patients developed ORN without having any evidence of previous trauma in several studies [8, 32, 58].

D) TUMOUR SIZE AND LOCATION

Differences in blood supply and anatomic structure between the mandible and maxilla may explain the overwhelming predilection for the mandible [66]. When located in the upper jaw, the ORN develops less progressively and the defects are less severe [86]. In the mandible, the buccal cortex in the premolar, molar, and

retromolar regions has been described as the most vulnerable site for radiation-induced vascular disease [87], because of its compact and dense nature [88]. This may be related to the decreased vascularity of this location, and also higher mineral content of the bone, which leads to a higher absorbed radiation dose [88]. Some studies found the molar area of the mandible to be most frequently affected [5, 66], whereas other found the symphysis [89], to be the site of ORN in 41 patients (73%). The presence of teeth and associated pathologic conditions did not explain the difference between the maxilla and the mandible and between areas in the mandible [5]. Some studies found that larger tumours were associated with a higher incidence of ORN [32, 34, 90], whilst others found no correlation at all [11, 29]. Probably the tumour location is more relevant then the tumour size. If a tumour is adjacent to bone, such as on the alveolus or in the mouth floor, there is an increased incidence of ORN [4].

E) TIME OF DEVELOPMENT OF OSTEORADIONECROSIS

The time interval between radiotherapy and the onset of ORN can be very variable, but the majority of the cases occur between 4 months and 3 years [5, 6, 24, 39]. Epstein et al. [58] showed that the time of developing ORN had an average of 4.5 months in the cases associated with dental/surgical trauma, and on the cases of spontaneous development, 50% developed it in 6 months, but it could be as long as 13 years. Berger and Symington [25] reported two very late cases, one after 45 years of radium implant therapy, and one after 38 years after external beam therapy.

Most cases commence in the first few years, and they include almost all of the spontaneously developing cases; however, the trauma-induced ORN may evolve an infinite number of years after radiation [5, 6]. The occurrence of ORN is not time dependent, so that it may become evident even years after radiotherapy [11].

F) ALCOHOL AND TOBACCO

Abuse of alcohol and tobacco is clearly identified as risk factor for ORN by several studies [5, 7, 10]. Their mode of action is unexplained. Furthermore, they probably potentiate the combined effects of other negative factors, such as contributing to poor oral hygiene. The vasoconstriction which occurs owing to smoking may enhance the occurrence of mandibular hypovascularization after radiotherapy [7].

Marx [91] found that 83% of his ORN patients continued their earlier smoking habit. In the study of Thorn et al. [5], 89% continued smoking.

G) CORRELATION WITH MORE ADVANCED TUMORS AND WITH TUMOR INVASION OF ADJACENT BONE

ORN has been correlated with more advanced tumors and with tumor invasion of adjacent bone [10, 11, 23, 29, 32, 58]. The study of Curi and Dib [34] showed no difference in ORN incidence when tumor size increased from Tl to T3. However, when the tumor invaded the adjacent bone, the number of ORN cases increased abruptly. All cases of T4-stage developed ORN in two cancer treatment conditions: patients with surgically unresectable tumors submitted to radiation therapy that resulted in ORN because of tumor necrosis, and patients submitted to surgical treatment followed by radiation therapy with insufficient time for wound healing. No difference was observed when the neck was N1, N2, or N3, but there was a significantly higher

incidence of ORN when the neck was N0. In long-term head and neck cancer follow-up, patients with no cervical metastases have a better prognosis than patients with cervical involvement and therefore are at higher risk to develop ORN [34].

H) BODY MASS INDEX

In the study of Goldwaser et al. [71], the body mass index (BMI) of patients who developed ORN averaged 23.02 while the BMI of those who did not averaged 25.13. On multivariate analysis, for every one point increase in BMI, ORN risk decreased by 27%. This association between increased BMI and lower incidence of ORN is important because the effects of surgery, radiation, and chemotherapy often compromise the nutritional status of these patients. In the study of Goldwaser et al. [71], compared with underweight patients, risk of ORN decreased by 50% in those with normal BMI, by 43% in overweight individuals, and by 37% in obese patients. However, the decrease in ORN rate was only statistically significant in the overweight group (P = .03). Mildly overweight patients may have had less severe disease, eg, smaller tumors and a lower incidence of metastatic disease and hence maintained their appetite and ability to eat during treatment. Though obese patients also exhibit sustained appetite and adequate nutrition, the additional comorbidities associated with obesity may increase the risk of ORN compared with mildly overweight patients. This study suggests that a higher BMI at any level protects against ORN, but not significantly so in the obese range.

I) USE OF ANTI-INFLAMMATORIES AND ANTICOAGULANTS

In the study Goldwaser et al. [71], it was demonstrated that 54% of non-ORN patients compared with 28% of the ORN patients took steroids before or after radiation therapy. On multivariate analysis, steroid use before or after radiation reduced the risk of ORN by 96%. These results support the “radiation-induced fibrosis” theory which occurs in 3 stages: 1) radiation damage of endothelial cells induces cytokine release, causing increased vascular permeability and exposure of subendothelium to blood products; inflammation and microvascular thrombosis ensue; 2) fibroblast activation, via interaction with reactive oxygen species created by radiation, leads to fibrosis and atrophy; and 3) necrosis [46]. The protective effect of steroids is not surprising based on this hypothesis. Their anti-inflammatory effects may inhibit the initial inflammatory phase of ORN, thereby preventing progression to thrombosis, atrophy, and necrosis. The finding that anticoagulant use significantly reduced ORN risk on univariate analysis also lends credibility to the radiation-induced fibrosis hypothesis. Prevention of thrombosis may be important in preserving the microvascular blood supply to radiated tissues. It should be noted that we included aspirin under the category of “anticoagulant,” so the benefit may result primarily from the anticoagulation effects, the anti-inflammatory effects, or both. The use of aspirin in radiated patients merits further exploration because of its wide availability, affordability, and low side effect profile compared with steroids.

CONCLUSIONS

During the past 80 years a number of theories about the pathogenesis of ORN have been proposed, with consequent implications for its treatment. Until recently tissue hypoxia and its consequences were accepted as the primary cause. A new theory for the pathogenesis of ORN has proposed that damage to bone is caused by radiation-induced fibrosis. Cells in bone are damaged as a result of acute inflammation, free radicals, and the chronic activation of fibroblasts by a series of growth factors. New treatments have therefore been devised.

ORN can lead to intolerable pain, fracture, sequestration of devitalized bone and fistulas, which makes oral feeding impossible [57]. ORN is an expensive disease to manage no matter what course of treatment is used. Effective management of any disease process initially requires diagnosis before treatment. Criteria used to identify ORN vary even among identical authors at different points in time. So, it is important to make a correct diagnosis before initiating a treatment.

A better understanding of risk factors for the development ORN and of the underlying pathophysiology may improve our ability to prevent this complication and help to improve the prognosis for those being treated for ORN.

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FIGURE CAPTIONS

Fig. 1 Initial mucosal breakdown with overlying necrotic bone

Fig. 2 Advanced mucosal breakdown with failure to heal with overlying necrotic bone

Fig. 3 Non-viable bone as demonstrated by lack of nucleoli in bone lacunae (L) and necrosis of bone marrow (NB)

Fig. 4 Radiation induced mucositis with incipient breakdown of the buccal mucosa

Fig. 5 Initial clinical signs of skin breakdown

Fig. 6 Initial clinical signs of skin breakdown

Fig. 7 Initial clinical signs of skin breakdown

Fig. 8 Skin breakdown and osteoradionecrosis of the mandibular angle and ascending ramus after radiotherapy for a parotid gland tumor

Fig. 9 Skin breakdown and osteoradionecrosis of the mandibular body

Fig. 10 Radiological aspects of osteoradionecrosis. Mixed radio-opaque radiolucent lesion, with the radiolucent areas representing bone destruction

Fig. 11 Axial CT of the mandible with osteoradionecrosis showing (a) small sequestra of bone and (b) symphysis pathological fracture