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ORIGINAL ARTICLE

Osteoradionecrosis of the jaws—a current overview—part 2: dental management and therapeutic options for treatment

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Abstract
Purpose The aim of this paper is to explore the current theories about pretreatment assessment and dental management of patients receiving head and neck radiotherapy, and the therapeutic options to treat osteoradionecrosis of the jaws, 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. Because most cases occur in patients who were dentulous in the mandible at tumor onset, proper dental management is the single most important factor in prevention.
Conclusions Complete dental clearance before treatment is no longer necessary. Controversy exists regarding the management of osteoradionecrosis of the maxillofacial skeleton because of the variability of this condition. The treatment of osteoradionecrosis has included local wound care, antibiotic therapy, surgical procedures, and the administration of hyperbaric oxygenation. Recently, new methods of treatment were introduced, according to the new theory about its pathophysiology.

Keywords Osteoradionecrosis · Jaw · Dental care · Treatment

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

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series of potential oro-facial complications. One of the worst complications is the osteoradionecrosis (ORN).

Since the therapy of ORN takes considerable time, implies a major capital outlay, and the outcome is unpredictable, the prophylaxis of this severe complication is a major goal in modern combined tumor therapy [1–3].

Because most ORN cases occur in patients who were dentulous in the mandible at tumor onset, proper dental management is the single most important factor in prevention. A significant challenge to the dentist is the determination, prior to radiation therapy, of what oral or dental condition pre-exists that requires treatment to limit the possibility of ORN following radiation therapy. Historically, the extraction of all teeth in the field of radiation was undertaken to prevent dental disease leading to ORN. This alone can be debilitating to the patient, both physically and emotionally [4].

It is now generally accepted that teeth in the high-dose irradiation field by no means inevitably need to be extracted, but all teeth with a limited prognosis or associated with active infection should be removed, allowing at least 2 or 3 weeks to elapse before radiotherapy is started to allow sound healing of the sockets. The dental conditions that are risk factors include unrestorable dental caries and moderate-severe periodontal disease [5, 6]. During treatment, close attention to oral hygiene is necessary with regular brushing and flossing, topical fluoride prophylaxis, and regular use of chlorhexidine mouth rinses [7].

ORN is a disease process with devitalization and devascularization of bone due to irradiation. Obliterative endarteritis, hyperemia, hyalinization, cellular loss, hypovascularization, thrombosis, and fibrosis are the most common histologic findings in ORN [8, 9]. These facts may result in metabolic and tissue homeostatic disturbances that decrease the diffusion of oxygen into the tissues and determine that ORN responds to different forms of treatment [8–10].

Lesions may respond with minimal conservative intervention [10–15], whereas some respond only to invasive surgery and hyperbaric oxygen therapy (HBO) [8, 16, 17]. Treatment of ORN varied extensively over the years. Due to the theory of radiation, trauma and infection, medical treatment with long term antibiotics and debridement was common for many years [18]. If this treatment failed, mandibulectomy was often the only solution [19]. Marx and Johnson [9] showed that HBO exposures on radiated tissue induce fibroplasias and angiogenesis. Pearlman et al. [20] used osteomyocutaneous flaps for mandibular reconstruction in irradiated patients. Later, techniques of microvascular flap surgery have been used to reconstruct severe contour deformities of the mandible after hemimandibulectomy and radiation therapy [21]. Based on current understanding of the pathophysiology of ORN, new protocols could be developed for its prevention and treatment [22]. Pentoxifylline, tocopherol, and clodronate are the indicated drugs, according to the theory of radiation-induced fibrosis [23].

The aims of treatment are the elimination of pain and associated infections, improvement of mouth function (opening, speech, and mastication), and the prevention of deformity (fistulas, bone exposures, bone defects, and pathological fractures).

In this paper, we explore the current theories about pretreatment assessment and dental management of patients receiving head and neck radiotherapy, and the therapeutic options to treat ORN, based on the literature review.

Pretreatment assessment and dental management of patients receiving head and neck radiotherapy

Periodontal tissue destruction caused by both poor oral hygiene and smoking after radiotherapy is a main risk factor and a critical acceleration factor in ORN [24].

Many authors have reported that the incidence rate of ORN decreases by performing dental management, including oral hygiene care [14, 25–27]. For this reason, the importance of good dental management and good oral health are emphasized to patients undergoing radiation for head and neck cancer [9, 28, 29].

It is important to consider that dental treatment in a patient planned to receive radiotherapy is singular, and may include dental extraction of a tooth that might otherwise receive a more conservative treatment [5, 30]. Although a conservative approach is indicated in some cases, for patients with limited past dental care, poor oral hygiene, and evident dental/periodontal diseases, a more aggressive pre-radiation dental management should be considered [5].

Since 1932, when Coutard [31] reported the Curie's Foundation experience with ORN, one finds that it has been noted to occur after dental extractions performed shortly before or at any time after radiotherapy. The incidence of ORN is three times higher in dentate than in edentulous patients, mainly as a result of trauma from tooth extraction and infection from periodontal disease [29, 32]. Morrish et al. [1] observed that patients who were edentulous at the time of diagnosis of cancer had a relatively low risk of developing ORN. Oral infections and trauma, including surgical intervention should therefore be kept to a minimum [33, 34]. The risk of developing ORN after an extraction is higher in posterior mandibular teeth with roots that lie below the mylohyoid line, and an atraumatic extraction is not possible [35].

However, caries (Fig. 1) and periodontal disease are common, and controversy has existed regarding whether such teeth should be removed. Forty years ago, it was recognized that the maintenance of a healthy dentition was essential for the prevention of ORN. This required the willing participation of a dentist to assess and monitor the

dentition and to remove teeth as necessary [36]. Prevention of ORN is primarily through meticulous attention to preradiation treatment planning to eliminate oral disease such as caries, abscess, and periodontal disease [4]. All teeth that were grossly carious, periodontally hopeless, or had a poor prognosis for retention beyond 12 months were removed before radiotherapy, with extractions after radiotherapy been avoided as much as possible [37]. Alveoloplasty with primary closure, the use of pre and post-operative antibiotics, and a 10-day wait before radiotherapy were recommended. Prevention also requires the patient to maintain excellent oral hygiene following radiation therapy. Additional preventive considerations include pilocarpine prescribed to assist salivary flow to minimize xerostomia, topical fluoride to control dental caries, and possibly the use of artificial salivary supplements [4].

It is now generally accepted that teeth in the high-dose irradiation field by no means inevitably need to be extracted. But patients elected to radiotherapy still need to receive preventive dental treatment. A study with 250 patients examined just before radiotherapy showed that 68% of them needed immediate dental care [38]. Even patients who regularly visit dental offices need specific dental care before radiotherapy, including dental extractions [30]. It is also desired that patients achieve a good level of oral hygiene before radiotherapy [39]. Dental extractions and periodontal treatment prior to radiotherapy prevent the development of radiation caries, progression of periodontal disease, and ORN [33]. The only teeth that really need to be extracted before radiotherapy are those teeth within the high-dose field that are unrestorable or that have advanced periodontal involvement, and those patients who are unwilling or unable to maintain oral care [14, 29]. Only non-totally erupted teeth with the risk of "hiding place" infections should be removed prior to radiotherapy, whereas totally impacted teeth should be left in situ [40]. Some authors recommend tooth extraction with periodontal pockets of >5 mm or >6 mm in high-dose radiated fields before irradiation [6]. All other teeth should be cleaned and restored before radiotherapy begins [26, 41]. This was shown by Bedwineck et al. [42], who published a paper comparing two protocols of teeth extraction. Between 1966 and 1969, the policy of the M.D. Anderson Hospital in Houston, Texas was to extract on an elective basis all teeth not in good condition. Between 1969 and 1971, the new policy was to conserve all teeth except those considered unsalvageable. The incidence of ORN dropped from 19.7% during the period of elective dental extractions to 7.9% during the conservation period (n=381). This decrease was due primarily to a reduction in the incidence of ORN precipitated by dental extractions (from 11.8% to 2.3%). According to Johnson (1997), mandibular teeth in bone to be radiated above 6,000 cGy are removed. An exception would be when there is excellent dental health and assured compliance.

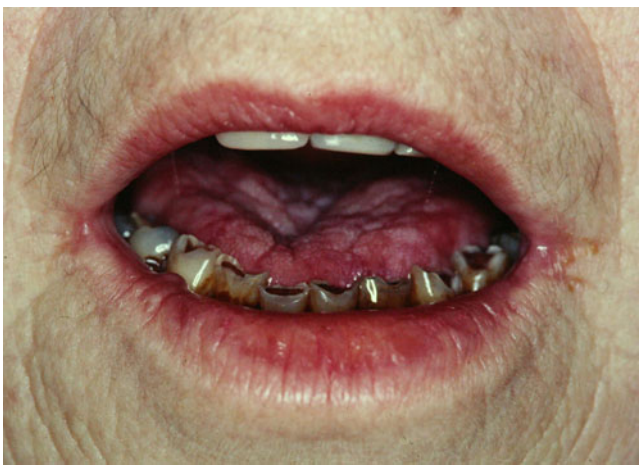

Fig. 1 Initial caries in the exposed dentin of the inferior teeth

Patients who receive high doses of radiation therapy should be submitted to dental extractions of all unrestorable teeth before radiotherapy [1, 43]. 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 [44]. 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 [45].

If the decision to extract teeth is made, the question is when to extract them, before, during, or after radiotherapy. The worst moment to extract tooth is considered to be during radiotherapy, but the common belief to delay extractions after radiotherapy, in anticipation of tissue recovery with time, is wrong [9]. The majority of the studies report a higher rate of ORN in post-radiotherapy extractions [9, 12, 13, 29, 43, 46, 47]. Although Bedwinek et al. [42] reported that extractions before irradiation increase the risk for ORN, most authors [12, 14, 46, 48] claim that the prophylactic removal of periodontally involved dentition that may absorb high doses of radiation and have a poor prognosis, particularly in the mandible, minimizes that risk. Beumer et al. [14] reported that ORN associated with postirradiation extraction more often requires radical resection than ORN associated with preirradiation extraction (45.4% versus 11.7%, respectively). One should conclude therefore that all teeth that are severely diseased should be extracted at the pre-radiotherapy appointment.

If pre-radiotherapy extractions are planned, the period between the extraction and the radiotherapy is critical. Marx and Johnson [9] and Epstein et al. [10] recommended an interval of 3 weeks before starting radiotherapy, since experimental work has shown that it takes 3 weeks for osteoid to form in the sockets, and epithelial repair to be complete after extractions [49]. However, this time period can sometimes delay treatment. Therefore, many authors

suggest a 2-week interval as acceptable, since this is usually the time needed to planning and mold room work [36, 50–52]. However, the repairing time should not be extended for a long period that compromises oncologic treatment and prognosis [9, 12, 46, 47, 51, 53]. The highest incidence of ORN is seen in those patients having extractions immediately prior to, or immediately after radiotherapy [46].

The technique used for planed pre-radiotherapy extractions includes alveoloplasty and primary closure [11, 46, 50–52, 54]. The mucoperiosteum overlying the alveolar bone to be removed must be elevated, but absolutely no more periosteal elevation should be done, as this will prejudice the blood supply of the underlying bone. Antibiotic therapy is usually indicated [36, 52, 55], usually lasting for 1-4 weeks.

If post-radiation extractions become necessary, the technique should be more conservative and must be executed with as little trauma as possible, and many recommendations have been done. Simple forceps extraction is suggested with due regard to not damage underlying bone [34]. Minimal trauma, alveolectomy with careful bone trimming, conservative flaps, primary closure without tension, and removal of few teeth per session minimize postoperative complications and are associated with lower ORN rates [12, 33, 40, 44, 46, 51, 53, 56]. Marx and Johnson [9] reported that there was a continuous loss of capillaries over time after radiation therapy, and advocated surgery 1-6 months after radiation therapy, to decrease the chances of ORN. Some have suggested that if the patient is felt to be at risk of ORN, hyperbaric oxygen therapy can be considered as prophylaxis against ORN [8, 10, 57]. In such cases, we would recommend the prophylactic use of ultrasound as alternative to hyperbaric oxygen [58].

The literature recommends antibiotics for exodontias associated with radiotherapy, especially in patients with risk of developing ORN. In general, the authors [12, 33, 44, 46, 51, 53, 59, 60] comment briefly on the general use of antibiotics without details about its type, posology, and time. In general, HBO and antibiotics have been considered favorable when used as adjuvants in dental extractions after radiotherapy, contributing to a low frequency of complications [45].

After radiation, there is a 5-6 month window of tissue repair and healing before the onset of the progressive fibrosis and loss of vascularity. During this healing phase, after the mucositis and dermatitis have resolved, is a much safer time to do necessary extractions, to decrease the chances of ORN [9]. Some have suggested that if the patient is felt to be at risk of ORN, hyperbaric oxygen therapy can be considered as prophylaxis against ORN [8, 10, 57]. In such cases, we would recommend the prophylactic use of ultrasound an alternative to hyperbaric oxygen [58].

Mealey et al. [48] reported that fully embedded teeth may not require removal if they are otherwise normal but that teeth that are partially erupted and exposed to the oral environment should be removed before radiotherapy. Hayward et al. [61] reported that impacted teeth can provide an infectious pathway to the jaw bone where reparative capacity has been impaired by the effects of irradiation. Although impacted third molars may remain asymptomatic throughout life, they are more likely to cause infections and lead to problems such as dental caries, cyst formation, and development of neoplastic lesions [62].

It is well accepted today that tooth extraction should be avoided even after many years of head and neck radiotherapy [60]. Decreased local vascularization and its consequent radiation impaired healing capacity, particularity in the mandible, is the main cause of ORN [3]. Important in prevention and management of ORN is recognizing the uniqueness of the radiation injury [63]. Even though cells vary in their sensitivity to radiation, all tissues in the field are injured to some degree. Some cells escape major damage, whereas others are killed outright and some die later from lethal damage. Still, others become incapable of replication. When cells are not replaced, there is a resultant loss of vascularity and cellularity that is progressive and unavoidable. The fact that soft tissue and bone become more hypoxic and fibrotic with time after high-dosage radiation has been reported by Marx [64]. Biopsy and tissue perfusion studies in radiated tissue over time show this lack of revascularization and a gradual loss of perfusion [9]. Clinical proof of this is tissue atrophy and induration, decreased jaw opening and swallowing difficulty, and the frequency of ORN years after completion of radiation. Radiated tissue has poorer quality the longer the elapsed time since completion of radiation and the risk for ORN is also greater with time. The wounding inherent in a tooth extraction even many years post-radiation submits this compromised tissue to metabolic demands to which it may not be able to respond [63].

Based on current understanding of the pathophysiology of ORN, the theory of radiation-induced fibrosis [23, 65–68], new protocols could be developed for its prevention and treatment. Previously, patients who required multiple dental extractions or extensive surgical extractions, or both, might have been given HBO before and after operation. Instead, all patients having dental extractions could be given 8 weeks of pentoxifylline 400 mg twice daily with tocopherol 1,000 IU, starting a week before the procedure. If ORN developed, then they could be continued for a further 6 months with clodronate prescribed after 3 months if there has been no appreciable response. The use of antibiotic prophylaxis before extractions, though commonplace, has not been validated in any study to our knowledge. However, antimicrobial propylaxis could be incorporated into this protocol if desired [22].

The role of infection in ORN is not clear, particularly as the transition between ORN and osteomyelitis is ambiguous, but recent reports have suggested that bacteria may have an

important role in its pathogenesis [69, 70]. Although the success of the pentoxifylline with tocopherol regimen seems to be successful, it is appropriate to give a short course of oral antibiotic for any extractions. Antibiotics should be used only for established ORN when there is clinical evidence of infection and frank pus, including discharging sinuses or collections [71].

Katsura et al. [24] have made a classification of the radiographic periodontal status after the radiotherapy that might help us define which tooth must and must not be extracted. It has three grades: (1) questionable change or none, (2) widening of periodontal ligament space and existence of lamina dura, and (3) widening of periodontal ligament space and disappearance of lamina dura.

The lamina dura is a compact bone surrounding the periodontal membrane, and it is identified as a well-defined radiolucent line in a panoramic radiograph. The periodontal membrane is a portal for bacteria to the mandibular bone in periodontal disease or in advanced dental caries. In the panoramic radiograph, periodontal disease or advanced dental caries initially manifest as an expansion of periodontal membrane. After further exacerbation affects the mandible, the rupture and disappearance of lamina dura may be evident [72]. Therefore, a grade 2 radiographic periodontal status (according to Katsura et al. [24]) means that bacterial infection has not yet spread to the mandibular bone, and a grade 3 status indicates that the infection has spread to the mandibular bone. In addition, it is speculated that the mandibular bone and the periodontal tissue in the radiation field are easily infected, because the blood vessels and bone cells usually appear to be damaged [24]. Some studies have reported that radiation actually weakens the periodontal tissue [73, 74]. In the results of Katsura et al. [24], all of the ORN cases had grade 3 radiographic status and >60% alveolar bone loss level at the onset of the condition, making these parameters as an indication for extraction before radiotherapy.

Extractions performed in radiotherapy patients should be done by a skilled surgeon, experienced with ORN [33, 36]. What number of teeth per quadrant should be removed at a single sitting, whether periosteum should be elevated, whether sockets should be closed primarily, whether radical or conservative alveoloplasty should be performed, and whether antibiotics should be used, have all been scrutinized in an attempt to reduce ORN after extractions. After 60 years, the issue remains unsettled, but all authors agree that the extraction technique should be as gentle as possible.

Since radiation-induced xerostomia is a primary causative factor in dental caries [75] and ultimately ORN, maintenance of a moist oral environment is crucial to the prevention of ORN [4]. Long-term damage to salivary glands resulting in permanent xerostomia is proportional to the exposure and the total volume of the glands irradiated. Secretion of saliva may be maintained at an acceptable level by limiting the radiation fields to the minimal volume consistent with effective treatment and wherever possible using planned fields to exclude at least part of the main glands [7]. Dry mouth may cause a subjective complaint of dry mouth, difficulty with speech and swallowing dry foods, a burning sensation in the mouth, dental caries, oral candidiasis, and bacterial sialadenitis. Gustatory (sugar-free chewing gum) or pharmacologic (cholinergic agents) stimuli may increase the functional activity of residual salivary tissue. Pilocarpine in doses of up to 5 mg three times daily can be effective. Patients with a dry mouth should avoid anything that further impairs salivation, such as drugs, tobacco, and alcohol. They may benefit from dietary control, taking frequent sips of water (particularly during eating), and using artificial saliva and topical fluorides [76].

According to oral health conditions, patient wishes, socioeconomic status, and prognosis of the cancer stage, a decision is made about the patient's dental management before starting radiation therapy.

Treatment

Conservative management

The initial approach to the treatment of ORN should be conservative, with medication and local wound care only, since up to 60% of the cases resolve thereby [1, 10, 13, 14, 25, 29, 39, 42]. This resolution rate may be over-estimated by including here figures of so-called 'mild' cases of ORN. Conservative approaches have also been cited to be wasteful of resources when ineffective, involving unacceptable amounts of time, effort, and medication [8].

Oral hygiene is essential, including the use of 0.02% aqueous chlorhexidine mouthwashes after meals [39] and constant saline mouthwashes. Debris should be washed/irrigated away and sequestra should be allowed to separate spontaneously or gently removed, since any surgical interference may encourage extension of the necrotic process. Curi and Dib [27] advocate sequestrectomy when a sequestrum is identified by radiologic techniques. Galler et al. [73] reported three cases of ORN which developed from periodontal disease activity, and proposed the use of chlorexidine digluconate and hyperbaric oxygen in the management of this condition. Analgesics and antiinflamatory drugs are prescribed when the physicians judged it necessary (increasing signs and symptoms of pain, discomfort, etc.).

A sequestrum is defined as a portion of bone that becomes separated from sound bone during the process of necrosis. Sequestration is a defense response in which granulation tissue and subsequent scar tissue wall off an

infected area. Significant amounts of necrotic tissue impair wound healing [8]. Most ORN lesions contain so great a quantity of necrotic bone that resorption and complete healing cannot occur [8]. Removal of sequestra facilitates secondary epithelialization and healing [11, 15]. Complete healing of osteonecrotic lesions after gentle or spontaneous removal of sequestra have been reported [12].

It is unreasonable to assume that sequestration alone contributes to complete recovery in all cases, because not all sequestrating lesions resolved in the cases of Wong et al. [77]. It appears that removal of sequestra does facilitate healing [11, 12] and is a guide to lesions that tend to respond most favorably to nonsurgical/HBO treatment.

Although ORN is not primarily an infectious process and the tissues are hypovascular, limiting the success of systemic antimicrobial agents, tetracyclines have been recommended because of their selective uptake by bone [11, 36]. However, access to avascular bone is questionable, making tetracycline inactive. Penicillin has also been used, because of the involvement of oral bacteria in the superficial contamination [55, 56]. Metronidazole, 200 mg, three times daily or other broad spectrum antimicrobials, could be added in cases of severe infection or where anaerobes are implicated [13, 15, 41]. Antibiotics rarely, if ever, cure ORN.

The use of packs over-exposed bone has been popular in the past [37]. He used zinc peroxide mixed with carboxymethylcellulose in hydrogen peroxide and also mentions the use of 5% neomycin solution or acriflavine as alternatives. Morton and Simpson [16] also recommended packs for covering small areas of exposed bone and delicate granulation tissue following separation of sequestrum, and for keeping necrotic bone cavities clean in patients who are not ready for definitive treatment. They found BIPP (bismuth and iodoform paraffin paste) on ribbon gauze very satisfactory, as it remains fairly soft and quite clean.

In the study of Wong et al. [77] (not including four patients who died with ORN), 19 (69%) of 28 patients had lesions resolve, stabilize, or improve, avoiding surgery or HBO. Identical conservative strategies have been reported by other studies to spare patients resection in 77-96% [10, 11, 14]. Where complete resolution is not achieved, asymptomatically preserved function may still be acceptable especially in patients with advancing age or those who wish to avoid surgery [10]. Complete resolution was experienced in 31-48% of patients [10, 12–14, 77].

An important management consideration is that most patients understandably wish to avoid additional major jaw surgery [78]. Morton and Simpson [16] remind us that all these patients have undergone treatment for malignant disease are elderly and are in poor health. For some patients, surgery is inappropriate, and they are more appropriately treated with conservative measures.

HBO therapy

Hyperbaric oxygenation is defined as a treatment where the patients breathes oxygen in a pressure chamber at 1.5 atmospheres or greater. The treatment may be delivered in a monoplace chamber pressurized with oxygen or in a larger, multiplace chamber pressurized with air, in which case the patient receives oxygen by mask, head tent, or endotracheal tube. HBO may have a significant role to play in the management of many conditions, including radiation necrosis of bone and soft tissues. Mainous et al. [79] in 1973 were probably the first authors to suggest the use of HBO therapy for the treatment of ORN.

HBO has revolutionized facial bone reconstruction in irradiated patients as it has made outcomes predictable and functional. If it is given preoperatively according to six rigid criteria, the success rates are more than 90%. The six criteria are: restoration of jaw continuity, restoration of alveolar bone height, restoration of osseous bulk, restoration of arch form, maintenance of bone, and restoration of facial contours [3].

ORN should be regarded as a chronic wound in which necrosis is compounded by hypoxia. Contamination by a variety of aerobic and anerobic organisms leads to infection which further enhances hypoxia and leads to further necrosis. HBO breaks the vicious circle in the following manner [80]:

1. by increasing tissue oxygenation through angiogenesis;
2. by controlling infection, predominantly through enhanced bacterial killing fungi macrophages and the production of bactericidal free radicals;
3. by stimulating fibroblast replication and development of a collagen matrix (healing).

The reason why the ORN does not heal is because metabolic demands for repair exceed the supply of oxygen and nutrition. The rationale for using HBO is that intermittent elevation of tissue oxygen tension stimulates collagen synthesis and fibroblastic proliferation [81], promote growth of new capillaries [81], and enhance the phagocytic ability of leucocytes [82]. HBO increases arterial blood oxygen tension level at least threefold compared with levels achieved during breathing 100% at sea level. Oxygen is transferred from the blood to tissues by diffusion, which depends on the oxygen tension gradient. Thus, more oxygen is transported into tissues under HBO therapy, even when the circulation is compromised but not totally absent [83]. It is also inhibitory to aerobic and anaerobic bacteria and inhibits bacterial toxin formation [84]. The daily elevation of oxygen tension in hypoxic bone and soft tissues result in the ingrowth of capillaries [85], fibroblastic proliferation [82], collagen synthesis [82], capillary angiogenesis [86], and enhances mineralization of bone in fractures [86].

Uncomplicated irradiated tissue, after the usual dose of 60–80 Gy for malignant tumors, has a capillary density only 20–40% of that of non-irradiated tissue [87]. HBO does not induce supervascularization in non-irradiated, otherwise normal tissue and therefore cannot be expected to accelerate healing in tissue in which the wound healing potential is not compromised [3].

Marx [8] introduced a protocol for the treatment of ORN that combines HBO therapy and surgery as its primary treatment modalities. He concluded that HBO alone cannot heal ORN wounds [46, 78, 88], suggesting that HBO without aggressive surgical management would not resolve the disease progress in most cases. The reasons showed for the low success rate were: (1) the degree of radiation tissue damage varies greatly between patients, even with identical doses and fractions, (2) HBO cannot resurrect dead bone, and (3) HBO cannot entirely reverse radiation injury. The use of HBO associated with surgery is commonly described in the literature [10, 17, 46, 78, 89]. It has concluded that only 'mild' cases of ORN can be cured with HBO, and the severe cases will need surgery to remove dead bone [17, 89].

The target tissue in HBO application is not the necrotic bone, but the compromised living tissue that is under great metabolic demands to simply remain viable [63]. HBO is adjunctive and not a "stand alone" therapy. When used alone without surgically removing necrotic bone, success rates are not greatly improved over local wound care or conservative therapy. HBO alone may arrest ORN only to have it recur later. HBO stimulation may also produce exuberant proliferation of granulation tissue, but this will be lost if the bone is dead [63].

Three reasons given by Marx [8] as reasons HBO is unable alone to consistently resolve ORN lesions also give us food for thought as to why nonsurgical/non-HBO methods are successful in certain circumstances. (1) Individual radiation effects are highly variable. Some patients have a greater residual and peripheral cellular pool after radiation. (2) Improvements in oxygen tensions with HBO are toward normal but do not reach those levels. Healing nonetheless can progress in suboptimal oxygen tensions. (3) HBO cannot resurrect dead bone. Some necrotic bone remains unresorbed because of hypovascularity. Sequestration removes this unperfused tissue. Gal et al. [90] also suggested that HBO therapy does not revive dead bone or resuscitate impaired bone, and, in advanced disease, will only delay more definitive therapy.

Postoperative HBO cannot be the treatment of choice if operation fails to treat ORN [3]. The purpose of hyperbaric therapy is to prepare the patient for surgical debridement and appropriate grafting, not to try to rescue poor results following the inappropriate use of surgery in the treatment of ORN [80]. If HBO is not given until after surgery, even if it begins the day after surgery, it will take a minimum of 2 weeks to have any clinical effect, during which time the tissues are severely compromised by hypoxia. To be effective, hyperbaric treatment must be given prior to surgery [80].

HBO therapy is not universally applicable. McKenzie et al. [89] reported 15% of 26 patients failed to complete HBO therapy because of lack of funds, noncompliance, inconvenience, and claustrophobia. Maxymiw et al. [51] cite that HBO is time-consuming and expensive. Marciani and Ownby [91] regard funding and availability of chambers as limitations to the general application of HBO. Epstein et al. [46] cite that prophylactic HBO for postradiation extractions would not be cost-effective.

Protocol

The protocols usually consist of 20–30 dives before and ten after tooth removal, with humidified pure oxygen administered at 2.0-2.5 atmospheres absolute pressure for 90–120 min each session, once a day [44, 47, 56, 92, 93].

A more specific protocol is not indicated. The pressure range suggested likely relates at least in part to historical practice differences between monoplace and multiplace hyperbaric chambers. In monoplace chambers not equipped for breaks of air breathing, continuous oxygen administration is often performed at 2.0 atmospheres absolute to minimize risk of central nervous system oxygen toxicity [94].

Contraindications and complications of hyperbaric oxygen therapy

Toxic effects are usually observed in the central nervous system and the main contraindications against the employment of HBO are some drugs, non-treated pneumothorax, neuritis, some forms of pulmonary disease, smoker's emphysema, and active viral infections [95, 96]. The only absolute contra-indications to HBO are optic neuritis, and existing neoplasia [97]. Although HBO may stimulate malignant growth, it is not contraindicated in patients with treated neoplasia [57]. HBO may be of use pre- and postoperatively in the patient with neoplasia both in primary and delayed reconstruction cases. Side effects of HBO are uncommon but include transient myopia, seizures, and otic or pulmonary barotrauma, the latter potentially leading to air embolism. Concern has been expressed that HBO may exacerbate a variety of autoimmune and immunosuppressive disorders, and viremia [95], but there is little supporting evidence.

Relative contraindications to HBO therapy include upper respiratory tract infection, chronic sinusitis, epilepsy, chronic obstructive airways disease, high fevers, a history of spontaneous pneumothorax or thoracic or ear surgery, viral infections, congenital spherocytosis, a history of optic

neuritis, and claustrophobia [39]. The risk from HBO therapy may be minimized by a careful pre-treatment assessment including chest radiography and electrocardiography; some advice also an otolaryngological and ophtalmological assessment [95].

The cost and lack of availability should also be mentioned as a potential problem related to HBO. HBO therapy is very time consuming, and therefore expensive. There are only few hospitals or diving centers with the facilities of a hyperbaric camera in each country. Therefore, it is not widely available, and can be even more expensive if the costs of travelling and accommodation are added.

Ultrasound therapy

Ultrasound has proved to be therapeutically valuable in many ways, including stimulation of tissue regeneration [98], increase blood flow in chronically ischemic muscles [99], protein synthesis in fibroblasts [100], healing of ischemic varicose ulcers [98], tendon repair [101], and angiogenesis in full thickness-excised incisions in the flank skin of adults rats [102] and in chick chorioallantoic membrane [103]. Local stimulation of fracture repair in rabbits and rabbits have also been evaluated [104–106]. Ultrasound was also used in human tibial fractures, in a prospective, randomized, double-blind evaluation. The results showed that the treated group had a significant decrease in the time to clinical healing [107].

Harris [15] was the first author to use therapeutic ultrasound for the treatment of mandibular ORN. This was based on previous uses of ultrasound as a simple means of promoting neovascularity and neocellularity in ischemic tissues [102]. Telfah [108] using near infrared spectroscopy has demonstrated that patients with ORN who received ultrasound therapy showed significant improvements of the metabolic activity (improvements of deoxyhaemoglobin concentrations). Figures 2, 3, and 4 show effects of treatment osteoradionecrosis with shortwave ultrasound before, 6 weeks, and 10 weeks after therapeutic ultrasound, respectively.

Surgery

Surgery is very often a treatment option for ORN. Usually, it is combined with antibiotics and mouth washes, and also with HBO and ultrasound.

Indications for surgical reconstruction include the presence of large intraoral ulcerations and/or fistula formation that leads to drainage and pain [109], as wells as radiographically evident osteolysis of the inferior mandibular border, and a pathological fracture, or orocutaneous fistula or both [3]. Surgical procedures may include intra- or extraoral decortization to control fistulae and removal

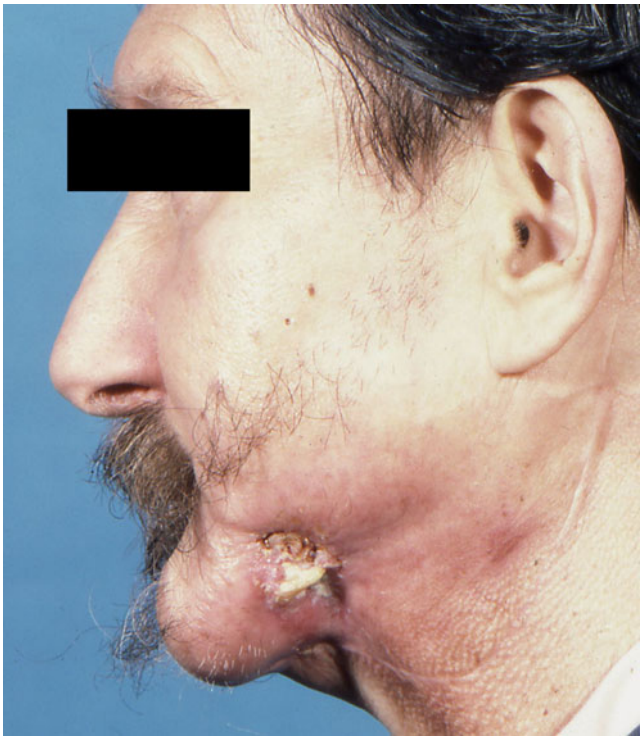

Fig. 2 Treatment of osteoradionecrosis with shortwave ultrasound (before ultrasound)

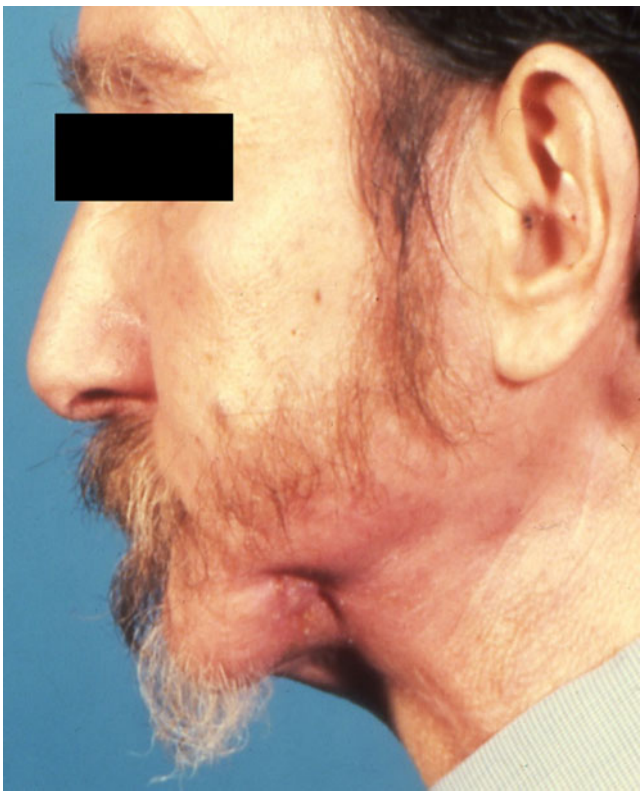

Fig. 3 Treatment of osteoradionecrosis with shortwave ultrasound (6 weeks after ultrasound)

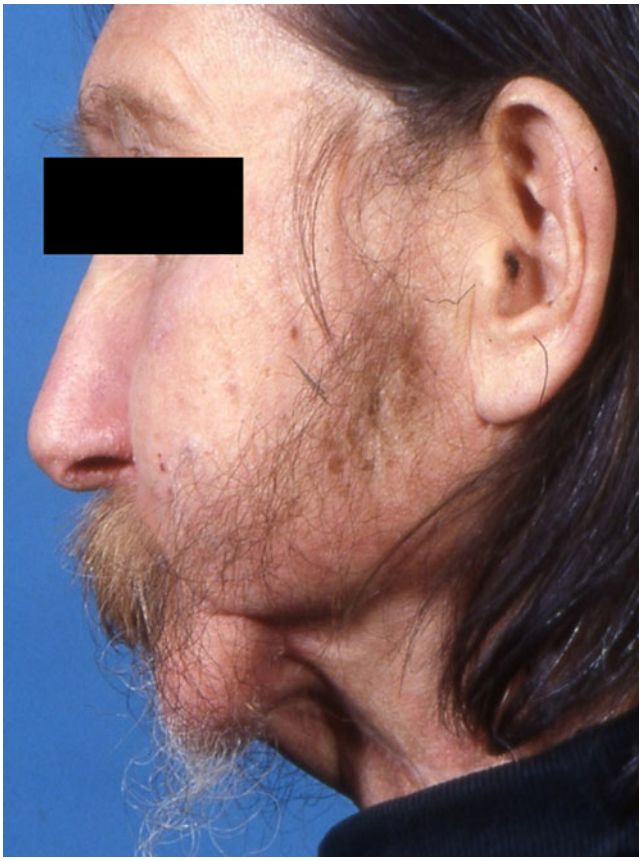

Fig. 4 Treatment of osteoradionecrosis with shortwave ultrasound (10 weeks after ultrasound)

of necrotic bone to expose the remaining vascularized irradiated bone. Figure 5 shows the clinical difference of normal bone (above) and necrotic bone (below). Bleeding provides the best guideline to the viability of the remaining tissue. Resection is usually necessary when there is a pathologic fracture, oral/cutaneous fistula, or full thickness osteolysis seen radiographically [8]. Until we have learned how to identify patients who can respond to HBO, this treatment should be the first choice in the treatment of ORN whenever possible [110].

The surgical options start with the removal of small sequestra, and increases depending on each case, to further sequestrectomy, alveolectomy with primary closure, closure of orocutaneous fistulae, and flaps to cover the area (local or free vascularized). In extreme cases, large resections and hemimandibulectomies are performed, and the bone should be reconstructed preferably with a bone source with its own blood supply, like fibula or iliac crest vascularized flaps. While surgery aims to remove frankly necrotic tissue, unless measures are taken to improve vascularity, healing will often be problematical [16].

Conservative surgical approaches start with small sequestra removal, and if needed, debridment of superficial bone until bleeding occurs. The cortical plates usually do not bleed in ORN patients. Drilling holes through the irradiated nonviable mandibular cortex was suggested by Hahn and Corgill [111] in an attempt to stimulate granulation tissue.

As ORN represents superficially contaminated bone with soft tissue radionecrosis as the major contributor to bone exposure and symptoms, the aim of the treatment can be limited to provide vascularized soft tissue to cover bone. The temporalis muscle flap can be used for the posterior oral cavity [15], and the nasolabial flap for anterior exposures. An alternative if these flaps are not available would be the use of distant myocutaneous flaps or free flaps, like the radial forearm free flap.

If ORN persists, mandibular resection can be indicated [11]. However, if reconstruction is not performed, collapse of the face can create severe functional disability and deformity, even knowing that the irradiated fibrotic soft tissues do help in reducing this tendency to collapse [16]. Mandibular reconstruction with bone grafts (Fig. 6) should be performed aiming the following criteria: restoration of bony continuity, alveolar height, facial form, and osseous bulk maintained over time and elimination of soft tissues deficiencies so that dentures can be worn [57]. The development of myocutaneous flaps and the use recently of microvascular free bone flaps allowed substantial

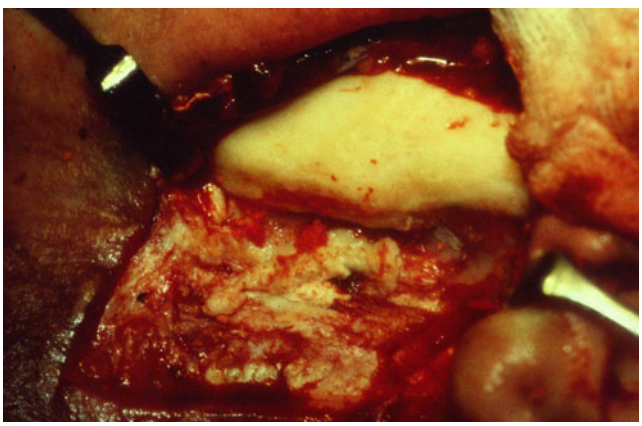

Fig. 5 Clinical appearance of normal bone (above) and necrotic bone (below)

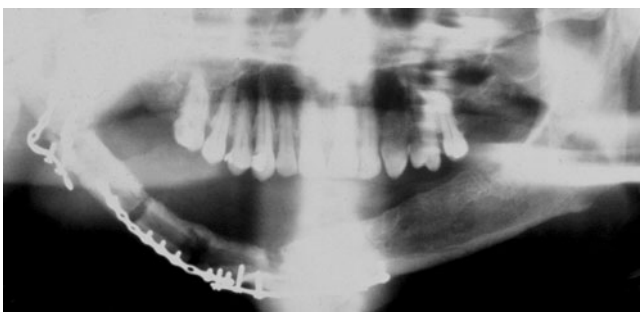

Fig. 6 Mandibular reconstruction with vascularized fibula bone grafts after partial resection

modifications in the decision-making process of the extent of the surgical ablation of an extensive ORN [112].

The introduction of well-vascularized tissue is needed to ensure the best functional reconstruction with optimal cosmetics. Buchbinder and St Hilaire [113] think that replacing the dead bone with a vascularized bone-containing flap is unquestionably the treatment of choice. This will not only allow for restoration of the mandibular continuity defect, but also will bring nonradiated soft tissue coverage with an intact blood supply.

The margins of the bony resection are estimated preoperatively with a computed tomography scan or magnetic resonance imaging, but the definite extent of the resection is determined intraoperatively with margins, whenever anatomically possible, that demonstrate healthy, bleeding bone [112, 113]. The affected soft tissue should also be excised.

Rehabilitation after reconstruction with osseointegrated implants can be used [114]. Many variables must be considered when planning whether or not to rehabilitate patients with an implant-supported dental prosthesis, such as the quality and quantity of bone, radiation status of the mandible in the areas selected to receive the implants, and financial resources to support this rehabilitation [115]. Marx and Johnson [9] showed in a study of serial biopsy specimens from irradiated patients that there was a continuous loss of capillaries over time after irradiation. Furthermore, there was no evidence of spontaneous revascularisation over time. Based on this study, these authors recommend that reconstruction or implant surgery should be performed from 1 to 6 months post-irradiation, because this interval reduced the risk of developing ORN. Figure 7 shows a case in which a conservative removal of necrotic bone was made. The mandible fractured later (Fig. 8), and a partial resection was made (Fig. 9). The patient is now waiting for reconstruction and rehabilitation. Figure 10 shows a patient who underwent complex mandibular resection after osteoradionecrosis and received a skin graft.

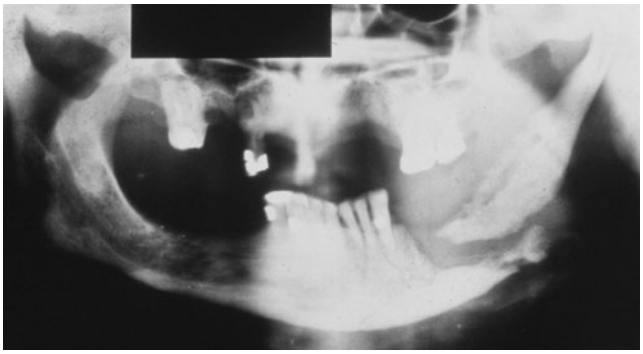

Fig. 8 Mandibular pathological fracture due to osteoradionecrosis

Treatment according to the radiation-induced fibrosis theory

To reverse changes in reactive oxygen species that produce radiation-induced fibrosis and ultimately ORN, new therapeutic regimens have been developed [68]. Pentoxifylline is a methylxanthine derivative that exerts an anti-TNFα effect, increases erythrocyte flexibility, dilates blood vessels, inhibits inflammatory reactions in vivo, inhibits proliferation of human dermal fibroblasts and the production of extracellular matrix, and increases collagenase activity in vitro. It is given with tocopherol (vitamin E), which scavenges the reactive oxygen species that were generated during oxidative stress by protecting cell membranes against peroxidation of lipids, partial inhibition of TGF-β1, and expression of procollagen genes, so reducing fibrosis. These two drugs act synergistically as potent antifibrotic agents. In animal studies, neither drug alone was capable of reversing reactive oxygen species [35].

The role of infection in ORN is not clear, particularly as the transition between ORN and osteomyelitis is ambiguous, but recent reports have suggested that bacteria may have an important role in its pathogenesis [69, 70]. Although the success of the pentoxifylline with tocopherol regimen seems

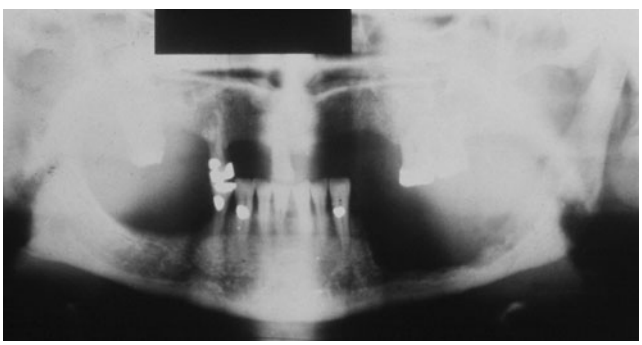

Fig. 7 Radiological aspect of conservative removal of necrotic bone in the mandible

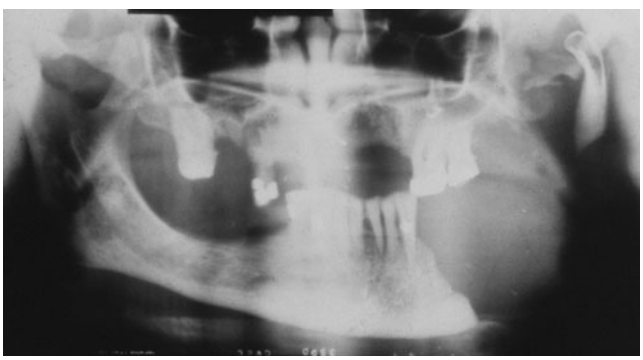

Fig. 9 Mandibular partial resection after pathological fracture

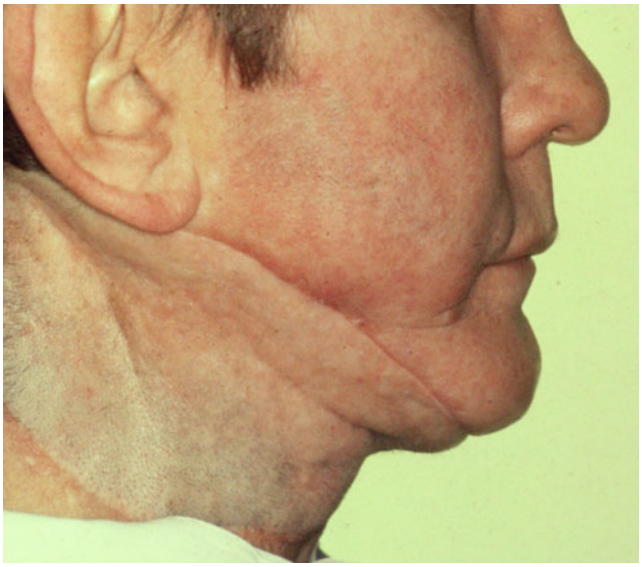

Fig. 10 Parietal skin graft after complex resection and reconstruction of osteoradionecrosis (same patient of the Fig. 6)

to be successful, it is appropriate to give a short course of oral antibiotic for any extractions. Antibiotics should be used only for established ORN when there is clinical evidence of infection and frank pus, including discharging sinuses or collections [71].

All patients having dental extractions could be given 8 weeks of pentoxifylline 400 mg twice daily with tocopherol 1,000 IU, starting a week before the procedure. If ORN developed, then they could be continued for a further 6 months with clodronate prescribed after 3 months if there has been no appreciable response [22].

Patients who would be excluded are those with pathological fractures, or in whom pathological fracture seem likely such as when free vascularized composite tissue transfer is planned in the short term. Patients who would have been given HBO before and after curettage or sequestrectomy should be given pentoxifylline and tocopherol [68].

Other treatment modalities

Other treatment modalities of ORN have been suggested. There are some interesting reports on drugs used to improve blood flow and tissue metabolism. Eppley et al. [116] suggested the use of fibroblast growth factor prior to bone grafting, showing improved vascularity in the irradiated soft tissue bed, and reduced risk of bone graft failure in rabbits. Dion et al. [117] used pentoxifylline to heal soft tissue radionecrosis wounds in the oral mucosa. Calcitonin has also been used successfully to treat ORN [118]. Electrotherapy [119] has also been suggested, but all these techniques have yet to be confirmed.

Conclusions

There is growing consensus that multidisciplinary teams can reduce the irradiation sequelae and that it is also mandatory that before radiation therapy for head and neck cancer, all patients undergo meticulous dental evaluation and rigorous follow-up during and after radiotherapy [1, 9, 33, 46, 47, 53].

Special attention must be paid to pre-treatment planning of dental therapy of patients undergoing radiotherapy of the head and neck region, and post-treatment controls. Particular care must be taken with extraction techniques, dental hygiene, fluoride devices for tooth protection, adequate healing time for teeth extracted before radiotherapy an exact pre-radiation planning of isodoses, and a careful post-surgical wound treatment. Antibiotics for prophylaxis of osteonecrosis are inferior to HBO treatment when performing minor elective procedures [47].

There are some topics in oral management to help preventing ORN:

1. All patients must receive explanations about the importance of periodic dental management to alleviate and prevent oral complications after radiotherapy, as well as tooth-brushing instruction before radiotherapy;
2. Extraction of diseased and at-risk teeth prior to radiation therapy. Diseased and at-risk teeth are described as those with caries extending into the pulp chamber, those with periapical lesions, periodontal pockets over 5-6 mm [6], furcation involvements of grade 2 and mobility of grade 2 or more. Extractions should be performed a minimum of 2 weeks prior to the beginning of radiation therapy [9, 10]. Teeth that should be treated are those within a field of radiation expected to exceed 50 Gy;
3. Patients who receive high doses of radiation therapy should be submitted to dental extractions of all unrestorable teeth before radiotherapy [1, 43]. 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 [44]. 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 [45];
4. Prescription of pilocarpine at a dose and schedule of 5 mg three times daily (up to 30 mg total daily dose) beginning 1 h prior to the first radiation dose and continuing potentially lifelong. Some evidence suggests that beginning pilocarpine prior to radiation therapy could lessen the need for the medication following radiation therapy [76];
5. Topical fluoride should be provided in a brush-on gel or in a custom tray and used once or twice daily for 15 min, and strict adherence to regular toothbrushing three times daily and flossing daily [4, 27];

6. Edentulous patients should be closely monitored for dehiscence or tissue breakdown of the mucosa under a denture. Denture ulcerations should be treated by leaving the denture out of the mouth until mucosal coverage is complete. Denture soft tissue adjustments and occlusion must be carefully monitored to minimize trauma. Following extractions and radiation therapy denture fabrication should be deferred up to a year or more depending on alveolar healing and overall oral and systemic health [4];
7. Saliva substitutes can be used to relieve xerostomia [76]. The subjective reports of some patients suggest that water has as much beneficial effect and is less costly than commercial products [4];
8. Scaling, measurement of the periodontal pocket depth, and plaque index after the radiotherapy once every 6 months and radiograph examination once every 12 months, to assess new possibilities of extractions [24];
9. All patients having dental extractions could be given 8 weeks of pentoxifylline 400 mg twice daily with tocopherol 1,000 IU, starting a week before the procedure. If ORN developed, then they could be continued for a further 6 months with clodronate prescribed after 3 months if there has been no appreciable response;
10. To perform dental extractions after radiotherapy when indicated, according to the classification of the radiographic periodontal status made by Katsura et al. [24] (grade 3 radiographic status and >60% alveolar bone loss level);
11. After radiation do the indicated extractions, when possible, preferably in the 5-6 month window of tissue repair and healing before the onset of the progressive fibrosis and loss of vascularity to decrease the chances of ORN [9].

Small lesions or those that produce sequestrum are clinical aspects of a future good prognosis that may heal after conservative management [27, 77]. Treatment of refractory and extensive ORN should include radical surgery and HBO therapy when it did not respond to conservative measures [78]. The fundamental principle for successful treatment of advanced ORN is the resection of all necrotic tissue with immediate composite osseous and soft tissue reconstruction. Radical resection and immediate microvascular reconstruction seems to be reliable and successful management for the advanced and extensive ORN of the mandible [112]. For advanced presentations of ORN including pathological fracture, fistula, and complete devitalisation of bone, segmental mandibular resection with free vascularized bone grafting has become standard treatment as it is increasingly clear that HBO alone is not beneficial [35, 112, 113].

The most effective method in our hands is a combined HBO/surgical protocol in which bone is removed, when necessary, only after revascularizing and improving the adjacent radiated tissue that is injured, but still living. The surgical removal of necrotic tissue is the focus: HBO is adjunctive. HBO alone seems to be ineffective in ORN because it is not able to revitalize dead bone [8, 56]. HBO in treating established ORN without aggressive surgical management is inadequate [10, 17, 44, 78, 89]. Therefore, it must be combined with a surgical approach to remove the devitalized tissues. It may help to reduce the need for major surgical interventions in patients whose cancer has healed [3]. When HBO is used it must be given in adequate dosage to be therapeutic.

Based on current understanding of the pathophysiology of ORN, new protocols could be developed for its prevention and treatment [22]. Pentoxifylline, tocopherol, and clodronate are the indicated drugs, according to the theory of radiation-induced fibrosis [23].

We would argue that it is better to rely on clinical observation to ensure optimum treatment rather than strictly follow a fixed number of protocol treatments. Prevention, however, should remain the goal of all who treat head and neck malignancies with radiotherapy [96].

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