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REVIEW PAPER

Osteoradionecrosis of the Jaws: Clinico-Therapeutic Management: A Literature Review and Update

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Abstract Osteoradionecrosis is one of the most serious oral complications of head and neck cancer treatment. It is a severe delayed radiation-induced injury, characterized by bone tissue necrosis and failure to heal for at least 3 months. In most cases osteoradionecrosis gradually progresses, becoming more extensive and painful that leads to infection and pathological fracture. The present paper provides a literature review and update on the risk factors underlying osteoradionecrosis, its clinical and diagnostic particulars, prevention and most widely accepted treatment options including the latest treatment modalities. Lastly, a new early management protocol is proposed based on the current clinical criteria relating to osteonecrosis secondary to treatment with bisphosphonates, together with the adoption of new therapies supported by increased levels of evidence.

Keywords Osteoradionecrosis · Etiology · Pathophysiology · Risk factors · Treatment options · Bisphosphonate osteonecrosis

Introduction

In 1922, Regaud published the first report about osteoradionecrosis (ORN) of the jaws after radiotherapy. Since then several theories have been propounded to explain its cause including the release of histamine, the theory of radiation, trauma and infection and until recently, the most widely accepted theory of hypoxia, hypovascularity and hypocellularity. There is a general consensus, however, about the clinical presentations of ORN, which are pain, drainage and fistulation of the mucosa or skin that is related to exposed bone in an area that has been irradiated [1]. Once ORN is recognised, it is irreversible and extremely difficult to treat. This paper describes the recommendations and current theories about its aetiology, pathogenesis and treatment.

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Definition

The most widely used definition of ORN that affects the jaws is based on clinical presentation and observation: irradiated bone becomes devitalized and exposed through the overlying skin or mucosa without healing for 3 months, without recurrence of the tumour [2].

Classification of Osteoradionecrosis

Together with the various evolving definitions of ORN, several classifications have been suggested. Some have attempted to derive a classification from Marx's treatment protocol, but this is not universally applicable as it uses the clinical response to HBO and surgical treatments that will not be used in all cases. The classification by Epstein et al. also requires knowledge of the clinical course, distinguishing those actively "progressing" from more chronic "persistent" cases. Instead, a simple, memorable, and immediate classification of mandibular ORN by Notani et al. which does not rely on any knowledge of clinical progress or response to treatment, is given in Table 1.

The classification by Epstein et al., requires knowledge of the clinical course, distinguishing those actively

Table 1 The Notani classification, is quickly applicable to all cases of mandibular osteoradionecrosis (ORN) after clinical examination and orthopantogram [29]

Notani class	Clinical features
I	ORN confined to dentoalveolar bone
II	ORN limited to dentoalveolar bone or mandible above the inferior dental canal, or both
III	ORN involving the mandible below the inferior dental canal, or pathological fracture, or skin fistula

Table 2 Epstein et al. [30], classification of osteoradionecrosis

Type I	Resolved, healed
	(A) No pathologic fracture
	(B) Pathological fracture
Type II	Chronic persistent (nonprogressive)
	(A) No pathologic fracture
	(B) Pathological fracture
Type III	Active progressive
	(A) No pathologic fracture
	(B) Pathological fracture

"progressing" from more chronic "persistent" cases, given in Table 2.

A more recent classification given by Lyons et al., which is based on the extent of the condition and its management is given in Table 3.

Epidemiology and Risk Factors for the Development of Osteoradionecrosis

Analysis of epidemiological studies of ORN does not provide accurate data about incidence and prevalence of ORN in the jaws because of the lack of agreement about its definition, inconsistencies in the length of follow-up between studies and limited data from prospective studies. ORN affects the mandible more often than the maxilla or any other bones of the head and neck [3]. Its incidence in the mandible is between 2 and 22 % of cases and it most often affects the body [4]. It is rare after radiation of less than 60 Gy, but more common when brachytherapy is used (the mandible must be in the area of treatment to be at risk). However, 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. Recent reports have suggested that when chemotherapy is added to radiotherapy the incidence of ORN may be increased whereas the use of intensity-modulated radiotherapy may reduce it [1].

Factors that Affect the Development of ORN

Size and site of the tumour, dose of radiation and type of mandibular resection, injury, or dental extractions, infection, immune deficiencies and malnutrition. Many patients with oral cancer have other serious diseases and have often had a long history of alcohol and tobacco misuse [5]. These, combined with poor nutrition and unsatisfactory oral hygiene, place such patients at high risk of developing ORN. Various factors associated with the development of ORN is given in Table 4 [6].

Dental disease and dentoalveolar surgery, in particular dental extractions after radiotherapy, are well-established predisposing factors to ORN; the documented incidence of ORN after extractions is about 5 %. 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 [1]. The risk of developing ORN after extractions is higher in posterior mandibular teeth with roots that lie below the mylohyoid line and when an atraumatic extraction was not possible [7].

Etiopathogenesis

Radiotherapy appears to cause ORN because it affects the small blood vessels of bone, inducing inflammation (endarteritis), which favors the generation of small thrombi that obliterate the vascular lumen and thus interrupt tissue

Table 3 Lyons et al. [31], classification of osteoradionecrosis

Stage	Description
1	<2.5 cm length of bone affected (damaged or exposed); asymptomatic. Medical treatment only
2	>2.5 cm length of bone; asymptomatic, including pathological fracture or involvement of inferior dental nerve or both. Medical treatment only unless there is dental sepsis or obviously loose, necrotic bone
3	>2.5 cm length of bone; symptomatic, but with no other features despite medical treatment. Consider debridement of loose or necrotic bone, and local pedicled flap
4	2.5 cm length of bone; pathological fracture, involvement of inferior dental nerve, or orocutaneous fistula, or a combination. Reconstruction with free flap if patient's overall condition allows

Table 4 Risk factors associated with the development of ORN

Primary site of tumor
Posterior mandible is more commonly affected by ORN because of its compact and dense nature
Proximity of tumor to bone
Extent of mandible included in primary radiation field
State of dentition—odontogenic and periodontal disease
Poor oral hygiene
Radiation dose >60 Gy
Use of brachytherapy
Nutritional status
Concomitant chemo-radiation
Ill-fitting tissue borne prosthesis resulting in chronic trauma
Acute trauma from surgical procedures to the jaw
Advanced stage tumors

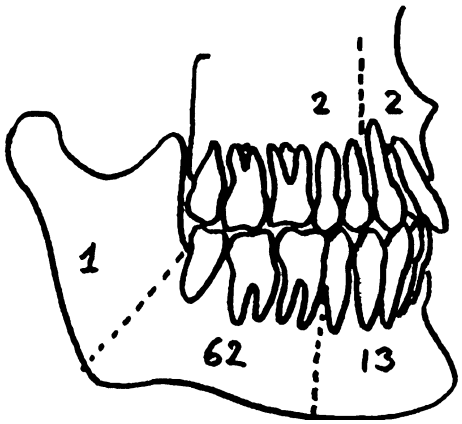

Fig. 1 Incidence of ORN among various sites of maxilla and mandible [8]

perfusion (Fig. 1). Likewise, radiation therapy produces an increase in free radicals and alters collagen synthesis. The bone loses its normal cellularity and undergoes fibrosis-atrophy with impairment of its repair and remodeling capacity. Under such conditions even minimal external trauma causes ulceration, facilitating contamination and infection and thus favoring bone necrosis. According to Marx, progressive hypoxia, hypovascularization and hypocellularity are observed in the affected bone (Table 5).

Theories of the Pathophysiology of Osteoradionecrosis

Watson and Scarborough reported three crucial factors in the development of ORN based purely on clinical observations; exposure to radiotherapy above a critical dose;

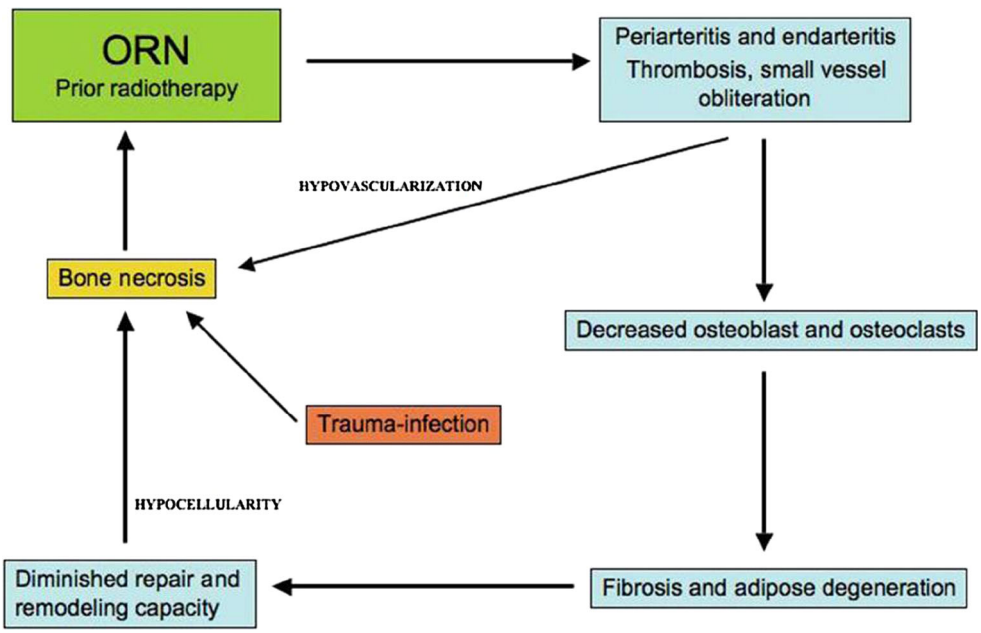

Fig. 2 Algorithm of ORN pathophysiology [16]

local injury; and infection [9]. 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 [10].

Meyer's theory: proposed his *radiation, trauma and infection theory*. He suggested that injury provided the opening for invasion of oral microbiological flora into the underlying irradiated bone. Meyer's theory lasted for a decade and became the foundation for the popular use of antibiotics with surgery to treat ORN [11].

Marx proposed the *hypoxic-hypocellular-hypovascular theory* as a new way of understanding the pathophysiology of ORN. Marx from his studies concluded that: "ORN is not a primary infection of irradiated bone, but a complex metabolic and homeostatic deficiency of tissue that is created by radiation-induced cellular injury; micro-organisms play only a contaminating role in ORN. The pathophysiological sequence suggested by Marx is: irradiation; formation of hypoxic-hypocellular, hypovascular tissue; and breakdown of tissue (cellular death and breakdown of collagen that exceeds cellular replication and synthesis) driven by persistent hypoxia that can cause a 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.

Radiation-Induced Fibroatrophic Theory

Radiation-induced fibrosis is a new theory that accounts for the damage to normal tissues, including bone, after radiotherapy. It was introduced in 2004 when recent advances in cellular and molecular biology explained the progression of microscopically observed ORN.

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.

Clinical Range of Osteoradionecrosis and Its Staging

Early ORN may be asymptomatic even though the main features of exposed devitalised bone through ulcerated mucosa or skin can be seen clearly. Pain is a common symptom and some patients have presented with intractable pain. Other associated symptoms include dysaesthesia, halitosis, dysgeusia and food impaction in the area of exposed sequestra [12, 13]. In severe cases, patients can

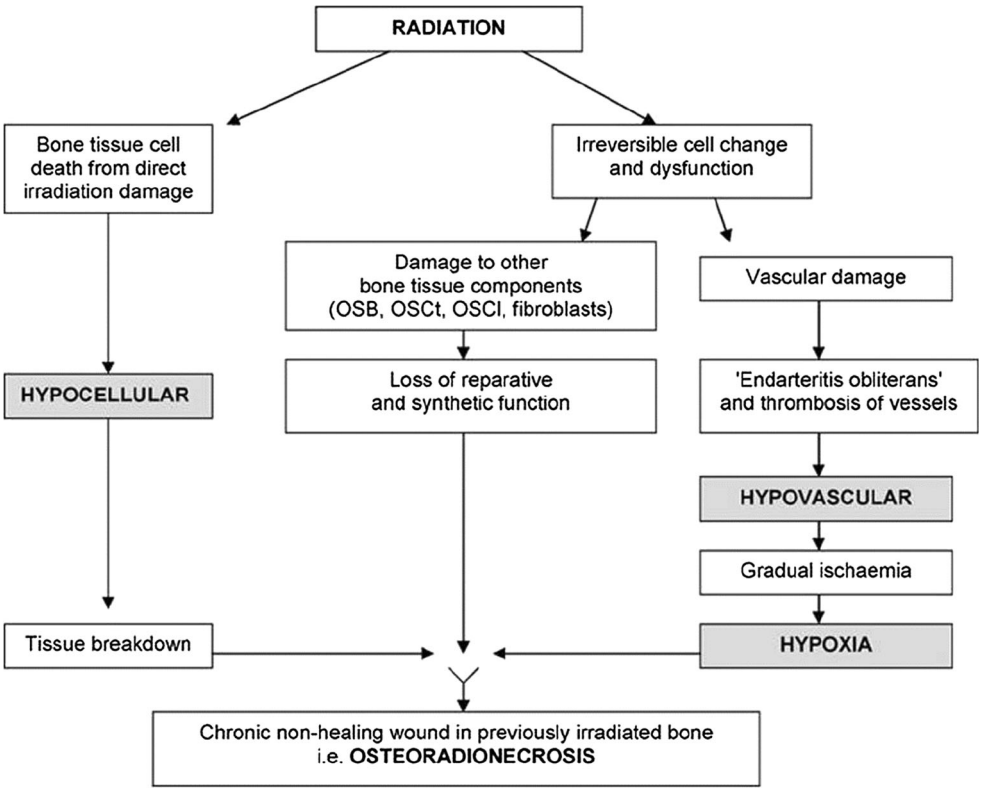

Fig. 3 Pathophysiology of ORN according to Marx [1]

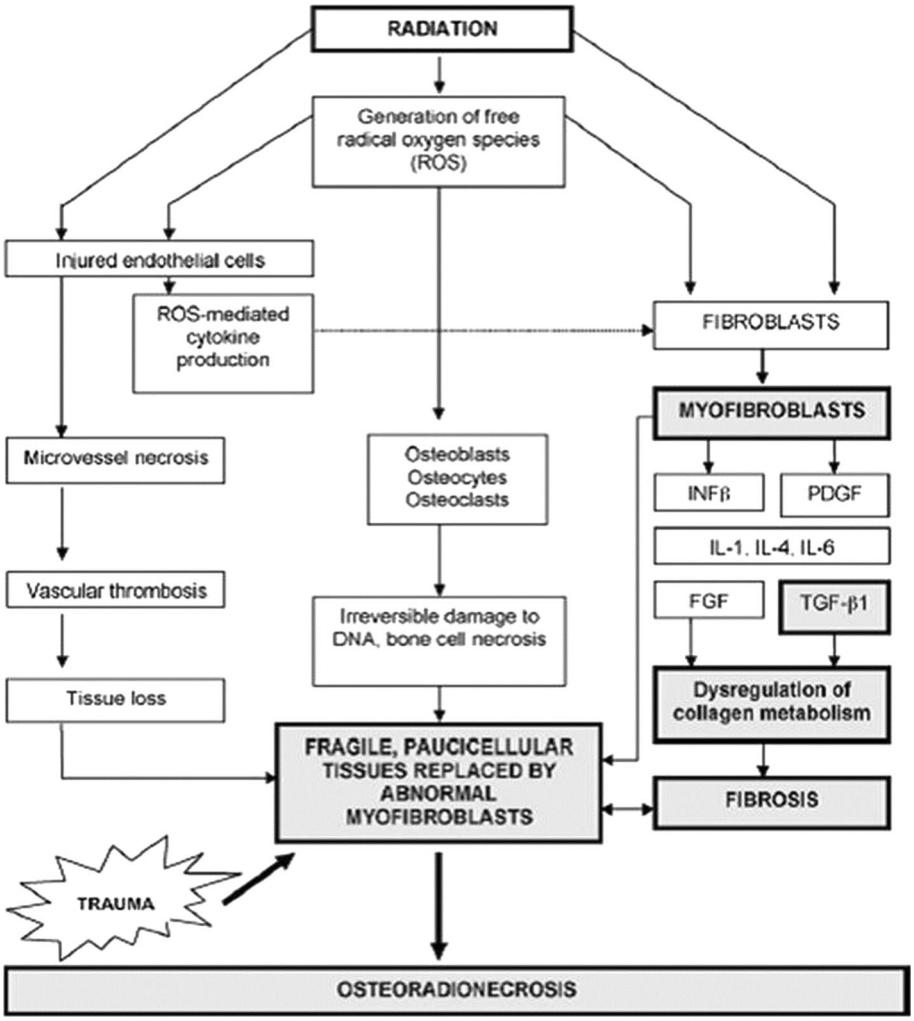

Fig. 4 Pathophysiology of ORN according to radiation induced fibro-atrophic theory [1]

present with fistulation from the oral mucosa or skin, complete devitalisation of bone and pathological fractures. The interval between radiotherapy and the onset of ORN can vary, but most occur between 4 months and 2 years. ORN usually develops during the first 6–12 months after radiotherapy. It may present much earlier after a local traumatic event. Epstein et al. [13], reported that ORN usually presented about 4.5 months after radiotherapy in cases associated with dental or surgical injury, but in most it may present after follow-up of the incidence studies. Over the years, many staging systems have been proposed to aid treatment and provide classifications for research. The classifications were based on various criteria, including the presence of soft tissue dehiscence necrotic bone, the amount of necrotic bone, oro-cutaneous fistulae and pathological fracture. The Wilford Hall hyperbaric oxygen ORN protocol proposed by Marx stages ORN in its response to his HBO treatment protocols [14]. The late effects on normal tissue (LENT) and subjective, objective, management and analytic (SOMA) scales proposed by the Radiation Therapy Oncology Group are scoring systems to stage the late complications of radiation and may also be used to stage ORN [15].

New Protocols for Prevention and Treatment of Osteoradionecrosis

Prevention

Preventive measures must be evaluated with a view to reducing the risk or severity of ORN. Deficient dental hygiene and septic mouth have been shown to increase the risk of osteoradionecrosis. Likewise, ORN is three times less frequent in edentulous patients than in patients who retain their teeth, possibly as a result of the trauma associated with the need for extractions after irradiation and the greater number of germs present. Before treatment, a thorough dental exploration is indicated, evaluating those teeth with a poor prognosis due to caries, periodontal

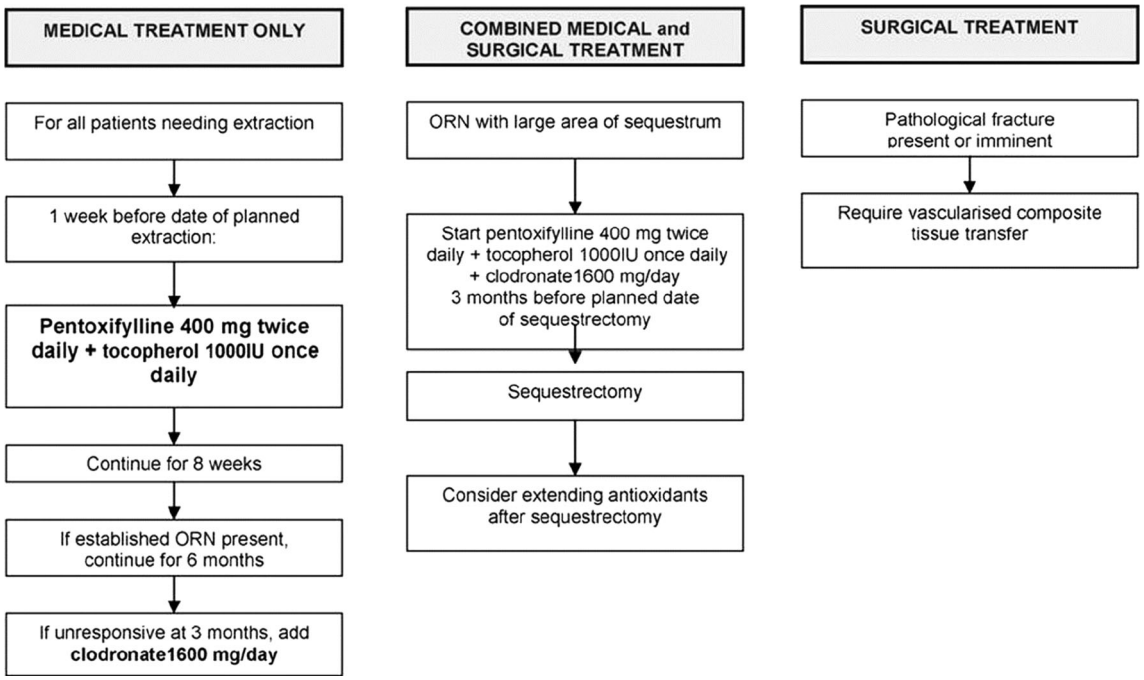

Fig. 5 Protocol for patients who require dental extractions after radiotherapy [1]

disease, or with latent infections. Repair should be limited to those teeth that are truly amenable to restoration and which have adequate chances for survival. In these cases extractions should be made at least 2–3 weeks before treatment. In the case of retained teeth, this period should be even longer. Another important consideration after treatment for lessening the risk of ORN is good fitting, support and stability of removable dentures, avoiding points of excessive pressure that may give rise to pressure ulcers [16, 17].

Less optimally, extractions can be performed within 4 months of completion of therapy. All patients should be instructed on meticulous oral hygiene and fluoride should be applied to the dentition daily via custom molded trays. Patients should undergo weekly checkups during radiation therapy and monthly thereafter for the first 6 months. Following this early post-treatment period, the patients should see their dentist every 4 months. The reason behind this ‘‘close follow-up’’ schedule is to monitor the patient’s compliance with meticulous oral hygiene and the daily application of topical fluoride. Cervical root caries, common in xerostomic patients, must be treated promptly in order to avoid involvement of the pulp chamber or undermining the structure of the clinical crown. Those who require dental extractions more than 4 months after radiation therapy should be treated with HBO. The Marx protocol of 20 dives at 2.4 atmospheres for 90 min per dive before extraction and ten dives after extraction has become the de facto standard.

Advances in the delivery of radiation therapy such as **intensity modulated radiation therapy (IMRT)** holds promise to decrease the incidence of osteoradionecrosis (ORN) by increasing the conformality of the high dose prescription to spare larger volumes of mandible and improve homogeneity of dose. The primary treatment factors that impact the probability of developing ORN include total dose of radiation (>60 Gy), volume of mandible receiving that dose, the part of the mandible that is irradiated and dose fractionation (fraction sizes > 2 Gy). Spontaneous ORN is associated with doses >60 Gy and can occur at a rate of 5–15 % with older techniques while newer techniques with three-dimensional (3D) conformal therapy and IMRT have decreased the rate to 6 % or less. A study comparing 3D and IMRT approaches, showed that when constrained appropriately, the volume of mandible receiving more than 50, 55 and 60 Gy could be decreased in oral cancer patients undergoing IMRT. In addition, there were fewer hot spots in the mandible and lower maximum dose. Several studies reporting the incidence of ORN after IMRT have been reported. The radiation therapy oncology group (RTOG-0022) study reported an incidence of 6 % ORN in oropharynx cancer patients treated at fraction size of 2.2–66 Gy without chemotherapy. The University of Michigan reported on 176 patients treated with IMRT. At a median follow-up of 34 months, no cases of ORN developed which they attribute not only to the conformality of IMRT, but also to meticulous dental hygiene as well as salivary gland sparing which may decrease the risk for

dental caries. Similarly Studer reported a 1.3 % incidence of ORN after parotid sparing IMRT. Thus, to date the best outcomes with IMRT with regard to ORN appear to be when the dose to organs at risk (mandible, oral cavity and parotid) are constrained, conventional fractionation is utilized, and meticulous dental hygiene is applied [6, 18].

Conservative Management of Osteoradionecrosis

"Conservative management" consists of local irrigation (saline solution, $NaHCO_3$, or chlorhexidine 0.2 %), systemic antibiotics in acute infectious episodes, avoidance of irritants (tobacco, alcohol, denture use) and oral hygiene instruction. "Simple management" refers to the gentle removal of sequestrum in sequestrating lesions (without local anesthetic) in addition to these conservative measures. Resection, HBO therapy, or both were initiated in cases of intractable pain, failure to respond to conservative measures and progressive deterioration (including pathologic fracture). Treatment duration terminated on the date of resection or first HBO dive [19].

Pentoxifyllin and Tocopherol in the Treatment of Osteoradionecrosis

To reverse changes in reactive oxygen species that produce radiation-induced fibrosis and ultimately ORN, new therapeutic regimens have been developed. Pentoxifylline is a methylxanthine derivative that exerts an anti-TNF_ 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-_1, and expression of procollagen genes, so reducing fibrosis. These two drugs act synergistically as potent antifibrotic agents. Treatment always consisted of pentoxifylline 400 mg twice daily and tocopherol 1000 IU once a day [20].

Hyperbaric Oxygen Therapy

The rationale for the use of hyperbaric oxygen (HBO) in radiation tissue damage is to revascularize irradiated tissues and to improve the fibroblastic cellular density, thus limiting the amount of nonviable tissue to be surgically removed, enhancing wound healing and preparing the tissues for reconstruction when indicated.

Marx and Ames first outlined a standard approach to the treatment of *established* osteonecrosis of the jaws with adjunctive HBOT. They proposed an approach which is known as the "Wilfred-Hall Protocol"; which consists of the three stages outlined below.

Stage I. Thirty consecutive treatments. If the wound shows no definitive clinical improvement, a further ten exposures are given, to a full course of 40 exposures. If there is failure to heal after 3 months, the condition is advanced to Stage II.

Stage II. The exposed bone is removed by alveolar sequestrectomy and further 20 HBO treatments are given, to a total of 60 exposures. If wound dehiscence or failure to heal occurs, the patient is advanced to Stage III.

Stage III. The criteria for this category are failure of Stage II, pathological fracture, orocutaneous fistula, or radiographic evidence of résorption to the inferior border of the mandible.

Recommended management commences with the 30-exposure protocol, along with surgical resection to bleeding bone and/or bony reconstruction, followed by soft tissue coverage. An additional ten treatments are recommended. If healing fails, additional surgery is carried out and ten further exposures to HBOT are given at that time [21]. Further evidence that HBO prophylaxis lowers the risk of ORN was found in Marx and Johnson tissue perfusion study.

Primary Outcomes of Marx Protocol (1999)

In 1999 Marx described two randomized control trial to measure the outcomes of HBO therapy. These trials reported data on two primary outcomes, postsurgical complication rate and, wound infection rate. All the patients in the trials required mandibular reconstruction in tissue beds exposed to ≥64 Gy radiotherapy using mesh trays with free soft tissue flaps/bone grafts. The intervention was 20 preoperative and ten postoperative HBO sessions (Figs. 2, 3, 4, 5).

The trials included 368 subjects, with 184 randomised to both HBOT and control groups. Overall, eight (6 %) people in the HBOT group suffered wound breakdown versus 37 (28 %) in the control group. Analysis for heterogeneity suggested a high proportion of variability between trials was not due to sampling variability ($I2 = 70$ %), and so this comparison was made using a random-effects model. There was a significantly improved chance of wound breakdown with control (RR 4.2; 95 % CI 1.1–16.8, $P = 0.04$ (Analysis 9.1). Stratification by tissue type involved confirmed that the direction of effect was the same for both studies, but it remained significant only for soft tissue flaps and grafts (RR following hemimandibulectomy 2.2; 95 % CI 0.8–5.9, $P = 0.12$; RR following soft tissue

flap or graft (8.7; 95 % CI 2.7–27.5, $P = 0.0002$). The number needed to treat to benefit with HBOT to avoid one wound dehiscence overall was 5 (95 % CI 1–59), and for soft tissue repairs alone was 4 (95 % CI 3–6) (Fig. 6).

Randomised Controlled Trials in HBO to Treat Osteoradionecrosis of the Mandible

To our knowledge the only randomised controlled trial in peer-reviewed publications for the use of HBO in the treatment of ORN in the head and neck region was by Annane et al. The trial had many laudable design features: it was a prospective, multi-centre, randomised, double-blind and placebo-controlled study carried out across 12 hospitals with an intended recruitment target of 222. The HBO protocol used 30 dives before and ten after operation at 2.4 atm. for 90 min, and so reflects the contemporary international consensus (if not the Wilford Hall protocol 4). However, the trial has proved controversial, with several different interpretations of the data possible, and despite serious voiced and published reservations about its design, has eroded enthusiasm for the role of HBO in the treatment of ORN. The principal finding was that HBO did not aid in the management of ORN, indeed an excess of poor outcomes in the HBO caused premature closure of the trial under early stopping rules. At 1 year, recovery in the HBO arm was 19 %, and 32 % in the placebo arm. This finding has now been cited by many health care funding bodies as evidence to withhold reimbursement for its use in the treatment of ORN. There are three main objections to the trial design. Firstly, the diagnosis, stage, and distribution of patients with ORN entered into the trial have been criticised, and the definition of ORN was imprecise compared with conventional clinical practice. Patients were included in the trial if they had one clinical change and one radiographic change. The clinical changes were pain, dysaesthesia in the distribution of the inferior alveolar nerve, bony exposure, trismus, or fistula. The radiographic changes were increased density, periosteal thickening, diffuse radiolucency, mottled areas of osteoporosis or sequestration. It can readily be appreciated that many patients who certainly *do not* have ORN would fit within these rather loose criteria. Patients with Notani III ORN (fracture or ORN at the lower border) were excluded from the trial; another factor that limited the usefulness of its findings. Stratification was not used so, of the small number ($n = 68$) actually randomised, a concentration of more severely affected cases could have been assigned to one arm or the other. The importance of this omission is exaggerated by the imprecise inclusion criteria. Interestingly the criteria for the measure of primary outcome were more robust; absence of pain, and exposed bone with stabilisation of radiographic findings. Although this gives confidence as to which patients had "real" ORN at the conclusion of the trial, we do not know who had it at entry. Data in the paper state clearly that only 38 of the 68 patients included actually had an area of exposed bone. Can there be confident interpretation of this trial, powered for inclusion of 222 patients, with data based on perhaps 38 "true" cases of ORN?

Hyperbaric Oxygen Therapy for Late Radiation Tissue Injury (LRTI)—Cochrane Review

Bennett et al. [22], conducted a systematic review by evaluating the quality of eleven relevant randomised

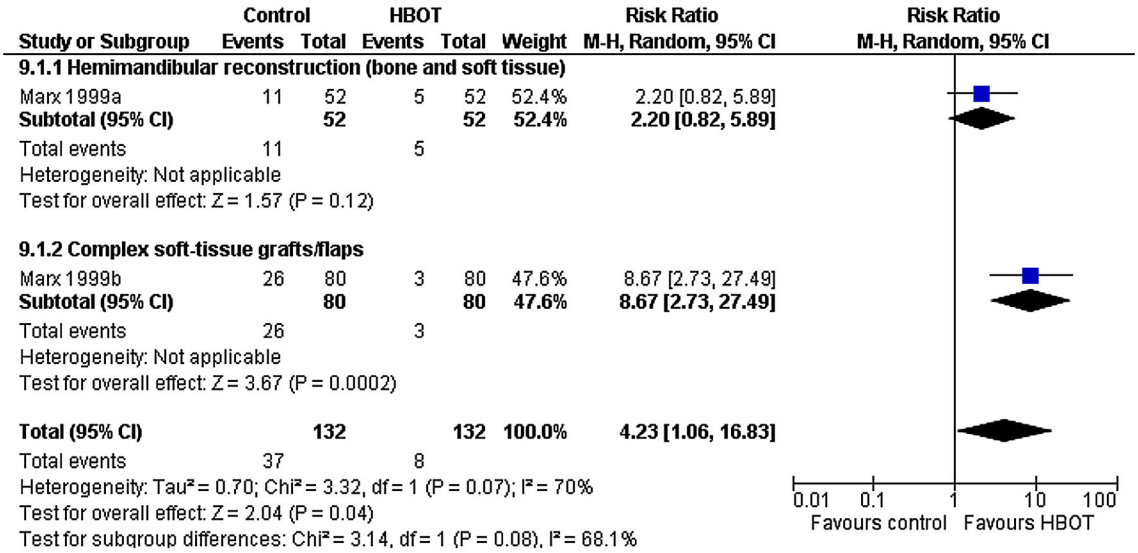

Fig. 6 Analysis showing primary outcomes of Marx protocol (1999) [29, 22]

control trails using the guidelines of the *Cochrane Handbook for Systematic Reviews of Interventions* and extracted the data from the included trials.

The review concluded that hyperbaric oxygen therapy (HBOT) has been suggested as a treatment for LRTI based upon the ability to improve the blood supply to these tissues. It is postulated that HBOT may result in both healing of tissues and the prevention of problems following surgery. There was no evidence of benefit in clinical outcomes with established radiation injury to neural tissue, and no data reported on the use of HBOT to treat other manifestations of LRTI. HBOT also appears to reduce the chance of ORN following tooth extraction in an irradiated field. The application of HBOT to selected patients and tissues may be justified [22].

Ultrasound for the Treatment of Osteoradionecrosis

Therapeutic US can exert its physical effects on the cells and tissues by thermal and non thermal mechanisms.

Thermal effects are used in physiotherapy for the treatment of acute injuries, strains, and pain relief. Nonthermal effects are used in the stimulation of tissue regeneration, healing of varicose ulcers, pressure sores, blood flow in chronically ischemic muscles, protein synthesis in fibroblasts, and tendon repair. Ultrasound affects bone by induction of bone formation in vitro and acceleration of bone repair in animals and humans. It has been shown that the nonthermal effects can result in healing of mandibular osteoradionecrosis. The principal value is the induction of angiogenesis, as shown by Young and Dyson. The new capillary formation involves activation, degradation of basement membrane, migration and proliferation of endothelial cells from preexisting venules, capillary tube formation, and maturation of new capillaries. Therapeutic angiogenesis is used to reduce unfavorable tissue effects caused by local hypoxia, including osteoradionecrosis, and to enhance tissue repair. Harrisll has suggested the use of ultrasound as an important means of revascularization of mandibular osteoradionecrosis. The patients were treated with ultrasound (3 MHz, pulsed 1:4, 1 W/cm) for 40 sessions of 15 min/day. Ten of 21 (48 %) cases showed healing when treated with debridement and ultrasound alone, 11 cases remained unhealed after ultrasound therapy and after debridement were covered with a local flap, and only one case needed mandibular resection and reconstruction [23].

Surgical Management

Major advances in the surgical management of ORN are related to reconstruction surgery. The development of myocutaneous flaps and the use of microvascular free bone flaps allowed substantial modifications in the decision-making process of the extent of the surgical ablation of extensive ORN. The replacement of the dead bone with a vascularized bone-containing flap will not only allow for restoration of the mandibular continuity but also bring non irradiated soft-tissue coverage with intact blood supply.

Commonly used flaps are fibular flap, ileac crest flap, scapular-parascapular flaps [24].

Treatment of Mandibular Osteoradionecrosis by Cancellous Bone Grafting

The use of a particulated cancellous bone and marrow (PCBM) graft after removal of necrotic bone is an interesting idea. Although it has been used in several other types of mandibular reconstruction, this is probably one of the first times it has been reported for ORN. However, stimulation of a new blood supply to the affected area is the main treatment goal and this has been proposed for a long time. Hahn and Corgill suggested creating holes in the affected area to stimulate granulation tissue in 1967. The use of PCBM for ORN has also been mentioned previously, but via an extraoral approach. Obwegeser and Sailer suggested bone grafting with autogenous decorticated iliac or rib via an intraoral approach. The use of tibia in this regard is new, but is there enough material for large defects. The clinical cases show excellent results, with good secondary healing. Perhaps the use of local vascular flaps could enhance these results, avoiding such high incidence of secondary healing. Placement of implants is easier and more predictable when this technique is used and that it should be done as a secondary procedure after the graft has taken [25].

Distraction Osteogenesis

Applicable for all distraction directions

- Indicated in case of poor surgical candidates for free flap transfer
- Increase bone quantity, improve bone quality and neovascularization
- Synergistic with HBOT, the use of BFGF and cyclic stretching (callus massage)
- Increase soft-tissue bed for further bone reconstruction [26].

Utilization of distraction osteogenesis (DO) in head and neck cancer is extremely appealing; patients could undergo large composite tissue resection and immediate soft tissue reconstruction with local flaps or microvascular free tissue

transfer. Flaps could be chosen on soft tissue coverage needs alone, without the need to incorporate bone. Postoperative radiation therapy would proceed sooner as the wound healing period would be truncated.

Replacement of bone through transport DO could be performed on an elective basis after completion of XRT (high dose highly fractionated radiation). For elderly patients or patients in whom microvascular free tissue transfer would pose an extreme health risk, DO alone might provide a less invasive alternative. DO could also provide an additional reconstructive option after flap failure, bone resorption or osteordionecrosis [27].

Bisphosphonates and Osteonecrosis of the Jaws

Osteonecrosis of the jaws is a recently described adverse side effect of bisphosphonate therapy. Patients with multiple myeloma and metastatic carcinoma to the skeleton who are receiving intravenous, nitrogen-containing bisphosphonates are at greatest risk for osteonecrosis of the jaws; these patients represent 94 % of published cases. The mandible is more commonly affected than the maxilla (2:1 ratio), and 60 % of cases are preceded by a dental surgical procedure. Oversuppression of bone turnover is probably the primary mechanism for the development of this condition, although there may be contributing comorbid factors. All sites of potential jaw infection should be eliminated before bisphosphonate therapy is initiated in these patients to reduce the necessity of subsequent dentoalveolar surgery. Conservative debridement of necrotic bone, pain control, infection management, use of antimicrobial oral rinses and withdrawal of bisphosphonates are preferable to aggressive surgical measures for treating this condition. The degree of risk for osteonecrosis in patients taking oral bisphosphonates, such as alendronate, for osteoporosis is uncertain and warrants careful monitoring [28].

Table 5 Management strategies in bisphosphonate osteonecrosis of the jaw (BONJ) [32]

Strategy	Treatment
Conservative management	Mouth wash and analgesia
Non surgical management	Antibiotics and antifungals
Surgical management	
Local intervention	No surgical flap
	Surgical flap
Radical intervention	Marginal resection
	Segmental resection
Adjunctive measures	Hyperbaric oxygen
	Parathyroid hormone
	Platelet rich plasma
	Laser
	Ozone

Discussion

ORN is still a serious complication resulting from radiotherapy and its incidence has not decreased in the last few years. Because ORN may be considered a nonhealing wound resulting from metabolic and tissue homeostatic disturbances, it responds to different forms of treatment. The incidence and the prevalence of ORN of the jaws after radiation therapy for head and neck cancer are unknown. Based on the literature, Clayman found an overall incidence of 11.8 % before 1968 and 5.4 % thereafter. Osteoradionecrosis (ORN) is characterized by delayed bone repair secondary to damage caused by radiotherapy (RT). The mean incidence of the disorder is 10 %, and it is particularly seen after traumatisms in the form of dental extractions—manifesting between 6 months and 5 years after radiotherapy (90 % of the lesions being located in the mandible).

The clinical management of ORN is difficult and normally comprises medical care, the avoidance of toxic habits, improvement of dental hygiene, the control of infections with antibiotics and antiseptics and removal of the necrotic tissue with more aggressive surgery once complications have appeared (pathological fractures). Some authors have preferred conservative treatment to control small necrotic areas, but this therapy may be insufficient in refractory and acute ORN. In addition, many clinical guides mention the possibility of employing hyperbaric oxygen therapy as a coadjuvant measure, though its use is controversial. Prospective random control trials conducted by Annane et al., Marx et al., and a recent Cochrane review by Bennet et al. [22], shows the effectiveness of HBO therapy in treatment of ORN. In any case, no general consensus-based clinico-therapeutic protocol has been established to deal with this disorder. The results of both a conservative approach and surgery/HBO treatment are well documented. In advanced conditions, the results of conservative treatment only are poor and under these circumstances radical resection of the involved segment and adjuvant HBO is a satisfactory option in the management of ORN of the jaws.

This article made an attempt to give a review on osteoradionecrosis regarding its etiology, clinical features, pathophysiology with most widely accepted theories and various treatment modalities depending upon the severity of the disease from conservative management, HBO therapy to recent treatment options such as ultrasound, treatment with antioxidants such as pentoxifylline and treatment with vitamin E, and reconstruction with vascularised bone flaps, treatment by distraction osteogenesis.

Conclusion

ORN can lead to intolerable pain, fracture, sequestration of devitalized bone and fistulas, which makes oral feeding impossible. 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.

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