CONCISE REVIEW

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# Osteoradionecrosis of the jaws: definition, epidemiology, staging and clinical and radiological findings. A concise review

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Osteoradionecrosis (ORN) of the jaws is a pernicious complication of radiation therapy for head and neck tumours. This article aims to provide an update on data related to the definition, epidemiology, staging, and clinical and radiological findings of ORN of the jaws. Using certain keywords, an electronic search was conducted spanning the period from January 1922 to April 2014 to identify the available related investigations. Pooled data were then analysed. ORN is described as exposed irradiated bone that fails to heal over a period of 3 months without evidence of persisting or recurrent tumour. The prevalence of ORN varies in the literature. Several staging or scoring systems of ORN have been proposed. Clinical findings include ulceration or necrosis of the mucosa with exposure of necrotic bone. Radiological findings are not evident in the early stages of ORN. Furthermore ORN may not be apparent in imaging even when the disease is advanced. Taking into account the severity of ORN and the difficulties in diagnosing it early and accurately, the clinician should be aware of this complex entity in order to prevent its appearance or the development of more severe complications.

***Key words:*** *Clinical findings, epidemiology, jaw, osteoradionecrosis, radiation therapy*

## INTRODUCTION

Osteoradionecrosis (ORN) is a pernicious complication of radiotherapy in head and neck cancer. It was first described by Regaud[1] in 1922 and is still a clinical challenge. According to the most recent literature, ORN of the jaws is defined as exposed irradiated bone that fails to heal over a period of 3 months without any evidence of persisting or recurrent tumour[2–4]. The mechanism of pathogenesis is still under investigation. However, the most frequently reported reason is radiation arteritis. Radiation arteritis leads to the development of a hypocellular, hypovascular and hypoxic environment, which results in a pathological outcome[5].

The purpose of this paper is to explore the current theories on the definition and staging systems of ORN of the jaws. In addition, the epidemiology and the clinical and radiological findings of ORN of the jaws, are critically reviewed based on the available literature. Finally, critical issues and considerations are discussed and pathways for future research are proposed.

## METHODS

An electronic search of three databases (PubMed, Scopus and the Cochrane Library) was performed using the keywords 'osteoradionecrosis', 'radiotherapy', 'osteonecrosis', 'osteoradionecrosis' and 'mandible', 'osteoradionecrosis' and 'jaw', 'osteoradionecrosis' and 'radiotherapy', 'osteoradionecrosis' and 'staging', 'osteoradionecrosis' and 'clinical findings', 'osteoradionecrosis' and 'radiological findings', to identify literature published in English and German between January 1922 and April 2014 (*Table 1*). Abstracts were obtained for all the titles identified during the electronic search. Two reviewers (A.C. and T.Z.) independently screened titles and abstracts to eliminate articles that were completely off-topic. No other exclusion criteria were utilised. Following exclusion of

**Table 1** Example of electronic search strategy in PubMed

| Search strategy | Results |
|---|---|
| Osteoradionecrosis | 1,980 |
| Radiotherapy | 286,652 |
| Osteonecrosis | 15,087 |
| Osteoradionecrosis and mandible | 636 |
| Osteoradionecrosis and jaw | 738 |
| Osteoradionecrosis and radiotherapy | 1,332 |
| Osteoradionecrosis and staging | 76 |
| Osteoradionecrosis and clinical findings | 177 |
| Osteoradionecrosis and radiological findings | 30 |

the articles irrelevant to the topic and the removal of duplicating papers, the remaining articles were carefully reviewed and their findings were critically analysed.

## RESULTS

### Definition

Several attempts have been made in order to define ORN. Ewing[6] was the first to use the term 'radiation osteitis' to describe changes in bone after radiotherapy. In the following years, several terms were used to name these changes in bone, such as radiation osteitis, ORN and avascular bone necrosis[7]. In 1974, Guttenberg[8] proposed the term 'septic ORN of the mandible' to describe the stage of necrosis when irradiated bone becomes superficially infected, ending up with a high risk of involvement of deeper structures.

In 1983, Marx[5] defined ORN as 'an area >1 cm of exposed bone in a field of irradiation that failed to show any evidence of healing for at least 6 months'. Marx also reported that superficial contamination and no interstitial infection was present. In 1987, Marx and Johnson[3] suggested the definition of ORN as: 'The exposure of nonviable bone which fails to heal without intervention'. Epstein *et al.*[9] defined ORN as 'an ulceration or necrosis of the mucous membrane, with exposure of necrotic bone for more than 3 months'.

Widmark *et al.*[10] described ORN as 'a non-healing mucosal or cutaneous ulcer with denuded bone, lasting for more than 3 months'. Both Widmark and Marx excluded from their definition conditions with necrotic bone for which the mucosa and skin were intact. Store and Boysen[11] reported that exposed bone is sporadically present; radiological findings are evident in all cases of ORN. In 1997, Wong *et al.*[12] defined ORN as 'a slow-healing radiation-induced ischemic necrosis of variable extent occurring in the absence of local primary tumor necrosis, recurrence or metastatic disease'.

According to the literature published in the last 15 years, ORN of the jaws is defined as exposed irradiated bone that fails to heal over a period of 3 months without evidence of persisting or recurrent tumour[2–4,13–15]. At the time of diagnosis, the necrosis might involve the bone superficially or deeply. It might be a process that progresses slowly or an active progressive state that can lead to a pathological fracture[16–18].

### Epidemiology

The prevalence of ORN varies widely in the literature (*Table 2*)[16,17,19–48] and ranges from 0.4% to 56%[19,20,22,24,30–33,36,49]. ORN usually affects patients over 55 years of age[14,36,50,51]. However, the most frequently reported prevalence rate is 5–15%[7,36,52]. In up to 20% of patients with persistent ORN which does not respond to aggressive treatment, bone damage is reported to be caused by recurrent disease or a second primary tumour[16,53].

### Staging

Several staging or scoring systems of ORN have been proposed (*Table 3*)[2,11,32,54–59]. These systems are based on response to hyperbaric oxygen (HBO) therapy, degree of bone damage, clinical–radiological findings, duration of bone exposure and treatment required.

Coffin[55] divided cases of ORN into two groups: minor and major. Morton and Simpson[56] subdivided ORN into three groups – 'minor', 'moderate' and 'major'. In 1983, Marx[2] proposed a three-stage system for ORN. According to his protocol, patients are categorised as Stage I if they exhibit exposed bone in a field of radiation that has failed to heal for at least 6 months and do not have a pathological fracture, cutaneous fistula or osteolysis to the inferior border. In Stage I, all patients receive 30 sessions of HBO at 2.4 atmospheres absolute for 90 minutes at depth. Patients who respond to HBO alone (Stage I responder) demonstrate a softening of the radiated tissues and spontaneous sequestration of exposed bone with formation of granulation tissue. Each Stage I responder undergoes an additional 10 HBO sessions and then the tissues are allowed to heal completely. Stage II patients are those who do not respond to the 30 sessions of HBO. This group is characterised by a large amount of non-viable bone that makes resorption and sequestration from HBO-induced angiogenesis alone impossible. Consequently, careful surgical debridement is required. Stage II patients undergo transoral resection with limited soft-tissue reflection. In particular, surgical treatment includes extraction of involved dentition and a non-continuity bone resection to clinically bleeding bone. Wound flaps are closed primarily and the patient is given 10 postsurgical sessions of HBO. Tissues that heal without

**Table 2** Incidence of osteoradionecrosis (ORN) in different studies

| Study | Year | Period | Total number of patients | Prevalence of ORN (%) | Mean irradiation dose |
|---|---|---|---|---|---|
| Watson and Scarborough[20] | 1938 | 1930–1937 | 1,819 | 12.9 | |
| Martin and Sugarbaker[21] | 1940 | | 103 | 25 | |
| MacComb[22] | 1962 | 1952–1959 | 251 | 37.1 | |
| MacDougall *et al.*[23] | 1963 | | 364 | 5 | |
| Grant and Fletcher[24] | 1966 | 1954–1962 | 176 | 37.5 | 10,000* |
| Rahn and Drane[25] | 1967 | 1960–1962 | 120 | 44.2 | |
| Rankow and Weissman[26] | 1971 | | 176 | 6.3 | 5,000* |
| Wang[27] | 1972 | | 262 | 5.8 | |
| Cheng and Wang[28] | 1974 | | 76 | 17.1 | 2,500* |
| Marciani and Plezia[29] | 1974 | | 220 | 10.5 | |
| Bedwinek *et al.*[30] | 1976 | 1966–1971 | 381 | 14.2 | 7,000* |
| Murray *et al.*[31] | 1980 | 1966–1975 | 653 | 21.1 | 5,000* |
| Morrish *et al.*[19] | 1981 | 1971–1977 | 100 | 22 | 7,500* |
| Epstein *et al.*[32] | 1987 | 1977–1984 | 1,000 | 2.7 | 6,000* |
| Withers *et al.*[33] | 1995 | 1976–1985 | 676 | 4.7 | 65† |
| Turner *et al.*[34] | 1996 | 1980–1987 | 333 | 5.9 | 55† |
| Thorn *et al.*[16] | 2000 | 1992–1998 | 80 | 74 | 60† |
| Storey *et al.*[35] | 2001 | 1965–1995 | 83 | 6 | 60† |
| Reuther *et al.*[36] | 2003 | 1969–1999 | 830 | 8.2 | 60† |
| Oh *et al.*[37] | 2004 | 1989–2004 | 81 | 4.9 | 52.6† |
| Studer *et al.*[38] | 2004 | 1980–1998 | 268 | 12.5 | 60† |
| Ben-David *et al.*[39] | 2007 | 1996–2005 | 176 | 0 | 65† |
| Jham *et al.*[40] | 2008 | 2003–2005 | 207 | 5.5 | 58.9† |
| Katsura *et al.*[41] | 2008 | 1996–2003 | 39 | 15 | 60.7† |
| Gomez *et al.*[42] | 2009 | 2000–2006 | 35 | 5 | 60† |
| Lee *et al.*[43] | 2009 | 1990–2000 | 198 | 6.6 | 60† |
| Stenson *et al.*[44] | 2010 | 1994–2008 | 27 | 18.4 | 62† |
| Gomez *et al.*[45] | 2011 | 2000–2007 | 168 | 1.2 | 67.9† |
| Monnier *et al.*[17] | 2011 | 2000–2007 | 73 | 40 | 66† |
| Crombie *et al.*[46] | 2012 | 2000–2007 | 54 | 36 | 69.7† |
| Niewald *et al.*[47] | 2013 | 1993–2001 | 99 | 12 | 72 |
| Tsai *et al.*[48] | 2013 | 2000–2008 | 402 | 7.5 | 70† |

*Radiation dose given in rads.
†Radiation dose given in Grays (Gy).

complication are treated with a prosthesis when required, similarly to Stage I responders. Stage III patients are characterised by having a large quantity of non-viable bone and/or soft tissue unable to be managed by HBO-induced angiogenesis alone or HBO combined with local sequestrectomy. In addition to 30 presurgical HBO treatments, each Stage III patient requires a continuity resection, stabilisation and 10 postsurgical sessions of HBO, and are scheduled for later (usually 3 months) reconstruction (Stage III-R). Stage III patients are therefore those who fail to respond to Stage I and Stage II treatment and those who initially present with a pathological fracture, cutaneous fistula or osteolysis to the inferior border[2,60].

Epstein *et al.*[32] suggested a new staging system for ORN with three tiers based on clinical findings. Glanzmann and Gratz[57] proposed a system based on the duration of bone exposure and necessity of treatment. Clayman[54] introduced a classification of ORN related to the integrity of the overlying mucosa. According to this classification, type I includes cases of ORN in which bone lysis occurs under intact gingiva or mucosa. Type II includes more aggressive cases of ORN in which soft tissues break down and the bone is exposed to saliva, causing secondary contamination. This is defined as radiation osteomyelitis. Type I cases heal with conservative therapy; type II cases do not. In 2000, Store and Boysen[16] introduced a new classification of ORN that is based on the presence or absence of clinical and radiological signs.

The most recently designed staging systems are these of Schwartz and Kagan[58] and Notani *et al.*[59] The system of Schwartz and Kagan[58] is based on clinical and radiological findings. Notani *et al.*[59] divided the cases into three grades based on the extent of the ORN lesion. Grade I is defined as ORN confined to the alveolar bone. Grade II is defined as ORN limited to the alveolar bone and/or the mandible above the level of the mandibular alveolar canal. In Grade III the ORN extends to the mandible under the level of the mandibular alveolar canal and a skin fistula and/or a pathological fracture is present.

## Clinical findings

Clinical signs and symptoms of ORN include ulceration or necrosis of the mucosa with exposure of necrotic bone for longer than 3 months, pain, trismus and suppuration in the area (*Figure 1a*)[32,61–64].

**Table 3** Classification systems of osteoradionecrosis (ORN)

| Study | Stages | | Description of stages | Basis of stage |
|---|---|---|---|---|
| Coffin[55] | 2 | Minor | A series of small sequestra which separate spontaneously after varying periods of weeks or months. These areas cannot be demonstrated radiologically | Clinical and radiological findings |
| | | Major | Necrosis occurring to an extent that involves the entire thickness of the jaw, and a pathological fracture is inevitable. This form can be obviously seen radiologically | |
| Marx[2] | 3 | Stage I | Exposed alveolar bone without pathologic fracture, which responds to HBO therapy | Response to HBO therapy |
| | | Stage II | Disease does not respond to HBO therapy, and requires sequestrectomy and saucerisation | |
| | | Stage III | Full-thickness bone damage or pathological fracture, usually requires complete resection and reconstruction with free tissue | |
| Morton and Simpson[56] | 3 | Minor | Ulceration with exposed bone and a history of bony spicules that healed spontaneously over a period of months | Clinical findings and response to treatment |
| | | Moderate | Exposed bone and small sequestra limited in nature and healing spontaneously with conservative treatment within 6–12 months | |
| | | Major | Large areas of exposed bone, with formation of large sequestra, possible fracture and sinus formation. These cases often require radical treatment | |
| Epstein *et al.*[32] | 3 | Stage I | Resolved, healed | Disease progression |
| | | Ia | No pathological fracture | |
| | | Ib | Pathological fracture | |
| | | Stage II | Chronic, persistent non-progressive | |
| | | IIa | No pathological fracture | |
| | | IIb | Pathological fracture | |
| | | Stage III | Active, progressive | |
| | | IIIa | No pathological fracture | |
| | | IIIb | Pathological fracture | |
| Glanzmann and Gratz[57] | 5 | Stage 1 | Bone exposure without signs of infection and persisting for at least 3 months | Duration of bone exposure and treatment necessity |
| | | Stage 2 | Bone exposure with signs of infection or sequester and without the signs of Grades 3–5 | |
| | | Stage 3 | Bone necrosis treated with mandibular resection with a satisfactory result | |
| | | Stage 4 | Bone necrosis with persisting problems despite mandibular resection | |
| | | Stage 5 | Death from ORN | |
| Clayman[54] | 2 | Type I | Bone lysis occurs under intact gingiva or mucosa | Clinical findings |
| | | Type II | A more aggressive type in which soft tissues break down, exposing the bone to saliva, and causing secondary contamination | |
| Store and Boysen[11] | 4 | Stage 0 | Mucosal defects only | Combination of radiological and clinical parameters |
| | | Stage 1 | Radiological evidence of necrotic bone with intact mucosa | |
| | | Stage 2 | Positive radiological findings with denuded bone intra-orally | |
| | | Stage 3 | Clinically exposed radionecrotic bone, verified by imaging techniques, along with skin fistulae and infection | |
| Schwartz and Kagan[58] | 3 | Stage I | Minimal soft-tissue ulceration and limited exposed cortical bone. Patients are treated with conservative management | Imaging and clinical findings |
| | | Stage II | Localised involvement of the mandibular cortex and underlying medullary bone | |
| | | IIa | Minimal soft tissue ulceration | |
| | | IIb | Presence of an oro-cutaneous fistula and mild soft-tissue necrosis | |
| | | Stage III | Full-thickness involvement of the bone, including the inferior border. Pathological fractures may also be present | |
| Notani *et al.*[59] | 3 | Stage I | ORN confined to alveolar bone | Clinical findings |
| | | Stage II | ORN limited to the alveolar bone and/or mandible above the level of the inferior alveolar canal | |
| | | Stage III | ORN involving the mandible below the level of the inferior alveolar canal and/or skin fistula and/or pathological fracture | |

HBO, hyperbaric oxygen.

Neurological symptoms, such as pain, dysaesthesia or anaesthesia, as well as fetor oris, dysgeusia and food impaction in the area, are also usually present. Exposure of rough and irregular bone can result in physical irritation of adjacent tissues. Progression of ORN may lead to pathological fractures, intra-oral or extra-oral fistulae and local or systemic infection. Difficulties in mouth opening, mastication and speech frequently arise[9,65–67]. In patients treated with external beam radiation therapy (EBRT), osseous alterations usually appear in the body of the mandible (premolar and molar regions), whereas in those managed with brachytherapy, the lingual or buccal surfaces are affected[68].

The diagnosis of septic ORN appears to be easier. Marked pain is the primary symptom. A thorough clinical examination will reveal intra- or extra-oral draining fistulae, ulcerations of the mucous

membrane, exposed devitalised bone, haemorrhage, cellulitis or pathological fractures. A biopsy is mandatory for final diagnosis in order to exclude metastatic cancer[8].

## Radiological findings

Radiographs, computed tomography (CT) scans, magnetic resonance imaging (MRI), Doppler ultrasound, nuclear medicine and near-infrared spectroscopy are often indicated in order to detect ORN[18].

ORN is not usually detectable radiographically in early stages[69]. Imaging features are not correlated to the severity of ORN[8,23,70,71]. The described radiographic features range from normal appearance, to localised osteolytic areas, extensive osteolytic areas, sequestra and fracture (*Figure 1b*). Radioluncies indicating post extraction sockets will often remain visible for longer than 12 months (*Figure 2a*). The most definitive radiographic alterations in early disease are increased radiodensity, as well as a mixed radio-opaque/radiolucent lesion in which radiolucent areas represent bone destruction (*Figure 2b*)[8].

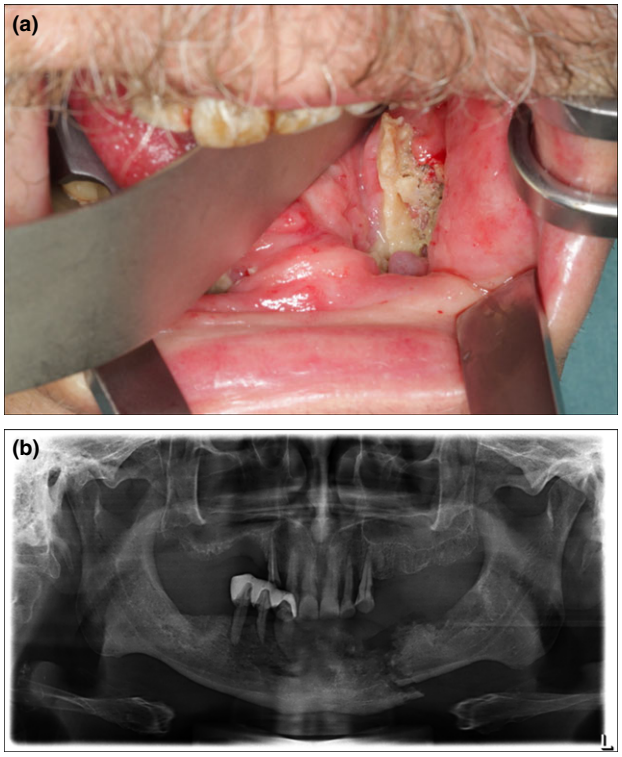


***Figure 1.*** A 69-year-old man presented with pain and a non-healing wound in the left lower jaw. The patient was an active smoker, suffered from pharynx cancer and had received radiotherapy (external beam radiotherapy with standard field sizes, conventional fractionation and mean dose 64 Gy) and chemotherapy. Clinically, exposed necrotic bone in the left lower jaw, inflammation, swelling and inferior alveolar nerve hypesthesia was present (a). The orthopantomogram revealed pathologic fracture of the left lower jaw (b). The patient was diagnosed with osteoradionecrosis of the lower jaw and was scheduled to be treated surgically.

Orthopantomogram (OPT) is the most frequently used imaging method for the diagnosis of ORN and is usually supplemented with other extra-oral or intra-oral radiographs. In an OPT, ORN is depicted as an undefined radiolucency, without sclerotic demarcation, which surrounds necrotic zone. Radiopaque areas can be identified when bone sequestra are formed. In order to be visible in an OPT, a substantial alteration in mineral content and extensive involvement of bone is required and this only occurs in later stages of ORN[9]. Ardran[72] noted that a 30% loss of bone mineral content is necessary before any radiographic change can be seen.

CT[73] shows osseous abnormalities, such as focal lytic areas, cortical interruptions and loss of the spongiosa trabeculation on the symptomatic side, frequently accompanied by soft-tissue thickening. Such a picture may cause difficulties in differential diagnosis between ORN and recurrent tumour[68]. In MRI with gadolinium administration, an abnormal marrow signal, cortical destruction and slight-to-mild irregular enhancement is demonstrated[35,74–76]. MRI has the advantage of excellent tissue contrast and high spatial resolution[77].

Bone scintigraphy permits estimation of the extension and location of the lesion. It shows high sensitivity (up to 100%) but low specificity (about 60%) for the diagnosis of ORN[77]. Scintigraphy using 99mTc-

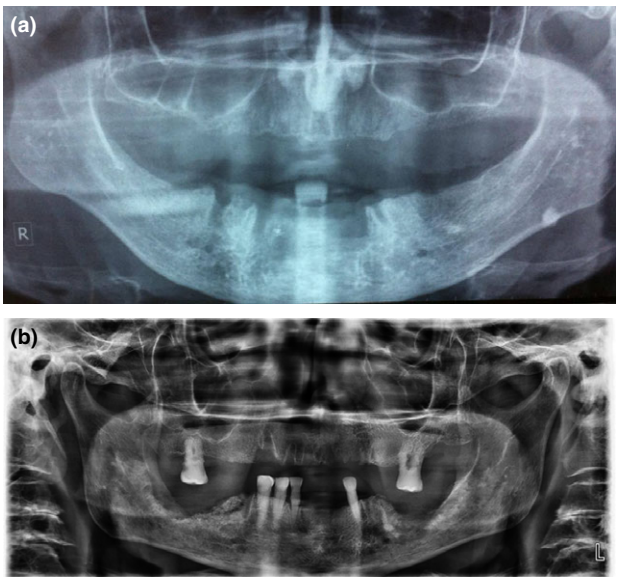


***Figure 2.*** Orhtopantomograms of patients who have received radiotherapy (external beam radiotherapy with standard field sizes, conventional fractionation and mean dose 64 Gy) for oropharyngeal cancers. The patients underwent extractions of teeth of the lower jaw after completion of radiotherapy. The orthopantomogram revealed radiolucencies indicating post extraction sockets, which remained visible for longer than 12 months (a), as well as increased radiodensity with mixed radio-opaque/radiolucent lesions, where the radiolucent areas represent bone destruction (b).

marked diphosphonates (99mTc-MDP) allows highly sensitive depiction of mandibular lesions as a result of their altered phosphate metabolism. Pathophysiological changes in bone can be identified sooner when using 99mTc-MDP than when using conventional radiography because scan changes reflect osteoblastic activity and good blood flow[78]. Low spatial resolution and over-projection by soft tissues are the major disadvantages of the method, which can be overcome with the use of single photon emission computed tomography (SPECT)[77]. Finally, positron emission tomography (PET), which is a promising method for pretherapeutic assessment of the spread of squamous cell carcinomas, has been advocated as being efficient for differentiating between ORN and tumour recurrence[79].

## Discussion and Conclusion

Irradiation of bone is the main prerequisite for development of ORN. A differential diagnosis is required to exclude recurrence of tumour and bisphosphonate-related osteonecrosis of the jaws. In contrast to the findings of Store and Boysen[11], mucosal breakdown or failure of healing is necessary for the diagnosis of ORN[3,9,10].

The duration of bone exposure is still a matter of controversy. Some authors did not state the period of time that bone was exposed[71]. Other authors recommended a 2-month period of exposed bone before diagnosis[73,80,81], or even 3[19,82,83] to 6[2,5] months. There are also cases in which a late diagnosis is present. Berger and Symington[84] reported two late presentations: one 45 years after radium implant therapy; and the other 38 years after external beam treatment.

A very short waiting period can lead to over-diagnosis as mucosal radionecrosis can occur without ORN. Moreover, any surgery and/or extraction usually takes up to 1 month to heal. On the other hand, monitoring a trauma for a longer period (such as 6 months) is contraindicated; intervention prior to this time is certainly needed. For the aforementioned reasons, in order to diagnose ORN, recent literature[2–4,13–15] indicates that bone exposure should be at least 3 months in duration.

The variability in prevalence of ORN can probably be attributed to differences in the study populations observation periods and existence of pretreatment dental assessment and dental management of cohorts. The literature reports numerous factors which are associated with the risk of ORN development and also affect its prevalence. Total radiation dose, brachytherapy, fractionation, poor oral hygiene, alcohol, tobacco use, dental extractions, tumour size and location, staging and chemotherapy have been highlighted[7,19,36,44,47,53,85–90].

The late onset of ORN can be attributed to the late occurrence of oropharyngeal cancers (OPCs) and their complications (mean age of patients over 60 years). This can be explained by the fact that oral tissues tend to undergo prolonged exposure to potential carcinogens with advancing age. In addition, aging cells may be more susceptible to DNA damage. ORN is predominant in the mandible (the ratio between ORN in the mandible and ORN in the maxilla is 24:1) [91]. The reason for this could be that the mandible has a restricted localised blood supply, which is often completely within the radiation field, whereas the maxilla has many anastomoses located outside the area of irradiation. Furthermore, mandibular bone density is different from maxillary bone density, and the mandible absorbs a higher amount of radiation during radiotherapy.

The prevalence of ORN has decreased since the 1990s[92]. Recent studies have shown a decrease in the prevalence of ORN to levels lower than 5%. According to Clayman[54], the application of megavoltage therapy resulted in a significant reduction of the overall prevalence of ORN from 11.8% before 1968 to 5.4% after this time. Wahl[93] described similar results and noted a prevalence of ORN of 3% during the period 1997 to 2006. Lee *et al.*[43] found that the frequency of ORN was 6.6% among 198 patients with either oral cavity or OPCs treated with radiation between 1990 and 2000. The overall reduction of ORN can be attributed to the advent of megavoltage radiotherapy, improved dental-preventive care and improved radiation techniques, including three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT)[7,36,38].

Marx's staging system[2] is based on the use of, and response to, HBO. The advantages of this protocol include selection of patients who are able to respond to less aggressive treatments, use of minimal levels of HBO, resolution of the disease and preparation of patients' tissues for reconstruction without further HBO[2,60].

Even though Marx's staging system is the one still used by surgeons, it has been used less frequently from the mid-1990s to date. The reasons for this are that HBO is nowadays recommended for use as adjuvant therapy, its effectiveness has been questioned and most cases of ORN can be managed successfully without HBO according to the most recent literature[58,94–96]. The staging system of Epstein *et al.*[32] is an improvement, but it is focussed on the presence or absence of a pathological fracture[58].

The classification system of Notani *et al.*[59] seems to be more accurate as it is based on: (i) the presence or absence of clinical and radiological signs, in contrast to other systems that are non-specific and are partly based on patients' subjective interpretation; and (ii) pretreatment evaluation, not on treatment response or

refractoriness. It is also simple and easily recalled[97]. (For review see Chronopoulos[98].)

During the past 80 years, a number of theories about the origin of ORN have been proposed. Despite the controversy, the majority of authors agree that prerequisites for the diagnosis of ORN are: (i) previous irradiation of the affected bone; (ii) absence of recurrent tumour; (iii) presence of mucosal breakdown or failure of healing, resulting in bone exposure; and (iv) 'necrosis' of the overlying bone. The presence of pathological fracture, fistula formation or cellulitis is not necessary for the diagnosis. Mandibular ORN is predominant over maxillary ORN. ORN can lead to pain, fracture and sequestration of the bone, as well as to fistulae. Although the prevalence of ORN has decreased to levels lower than 5%, it still remains a pernicious complication of radiotherapy and a challenge to the clinician because of difficulty in its management. Owing to the severity of ORN and the difficulties in its early and accurate diagnosis and treatment, increased awareness of this complex entity among clinicians is desirable, with the aim to prevent its appearance or the development of severe complications. Further research is required in order to clarify its complex etiology, and guide new treatment strategies.

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## Conflicts of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. There was no funding received for this study.

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