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Review

New classification system for osteoradionecrosis of the jaws — An integrative review

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Abstract

The aim of this paper was to present an overview of the previous published classification and staging systems for osteoradionecrosis (ORN) of the jaws and propose a new classification system for ORN. An electronic search was conducted using Medical Subject Headings (MeSH) terms, 'osteoradionecrosis' and 'classification', and free text words, 'stage', 'staging', 'ORN', classification'. A total of 2053 manuscripts were identified, of which 21 were included, reviewed, and analysed by all authors. A total of 21 different classification and staging systems were identified. Objective findings, included exposed bone and/or fistula, as well as radiological evidence of pathological fracture, were the three most used factors in the existing classification and staging systems (57.1%, 38%, 52.4%). Nine classification and staging systems (42.9%) were treatment-dependent. Fourteen out of the 21 (66.7%) classification and staging systems only described changes in the mandible. Notably, only one article described changes in the maxilla. No standardised classification or staging system has to our knowledge addressed the complexity of ORN. There is a clear need for a new classification and staging system that enables the monitoring of disease progression, evaluation of treatment outcomes, restaging, and comparison of different treatment approaches. We propose a new classification system to address these unmet needs.

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Introduction

Osteoradionecrosis (ORN) of the jaw is a well-known, serious complication of radiotherapy (RT)¹ and one of the worst post-irradiation late sequelae in individual patients.² ORN is primarily diagnosed based on objective clinical signs and subjective symptoms such as infection, pain, exposed bone, and radiological findings.³ The effects of irradiation (from 30 Gy to > 66 Gy) on the jaws lead to a lifelong risk for the development of ORN.⁴

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Definition and incidence

ORN was first described by Regaud in 1922.⁵ Today, ORN is defined as exposed, necrotic bone within the radiation field where tumour recurrence has been excluded.^{6–13}

The incidence of ORN shows great variability in the literature, ranging from 2% to 28%. ^{6,8,11,12,14,15} The implementation of intensity-modulated radiotherapy (IMRT) has further reduced the incidence of ORN compared with 3D-conformal radiotherapy. ¹⁶

Structural radiological bony changes are generally delayed, and studies have shown that a bone mineral loss of $30\% \pm 50\%$ is required, before it is visible on orthopantomography. Therefore, ORN is expected to be underdiagnosed if radiography is the only diagnostic tool.

Pathophysiology

In 1983, Marx ¹⁸ proposed a new concept of ORN pathophysiology based on the triad of hypoxia, hypocellularity, and hypovascularity. Marx also suggested that microorganisms are mainly surface contaminants and that ORN is a problem

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of reduced wound healing rather than primary infection. ¹⁸ In 2004, Delanian presented another theory of late radiationinduced fibroatrophy (RIF), which is occasional irreversible damage after radiotherapy. 19 The exact aetiology remains unclear; however, there is a high possibility that hypoxia, hypocellularity, hypovascularity, and radiation-induced fibroatrophy coexist.

Despite the existence of numerous classification systems for osteoradionecrosis (ORN), none has gained international acceptance. The lack of standardisation hinders consistent monitoring of disease progression and limits meaningful comparison of treatment outcomes. This work was undertaken to critically review the existing systems and to provide the foundation for a more clinically useful and standardised classification.

This study aimed to present an overview of published ORN definitions, classifications, and staging systems for patients with ORN after previous radiotherapy for head and neck cancer. The secondary aim was to develop a new classification system for all aspects of ORN.

Methods

ORN

An electronic search of two databases (PubMed and the Cochrane Library) was performed using MeSH terms, 'osteoradionecrosis' and 'classification', and free text words, 'stage', 'staging', 'ORN', classification' to identify literature published up to today (Fig. 1). The inclusion criterion was literature containing ORN classification and staging. The exclusion criteria were languages other than English and duplicate studies. The search was conducted on February 7, 2024, by one reviewer (SWMA) and yielded 2069 manuscripts in the English language. These numbers were reduced to 751 after duplicates were removed. Screening the abstracts and titles yielded 10 papers, and after cross-checking by scanning their reference lists, we obtained 21 articles that were critically read and analysed by all the authors.

Results

An overview of the factors included in the various classification and staging systems is presented in Table 1. None of the articles in the reviewed literature included subjective signs such as sensibility disturbances or radiological findings such as dental pathology. These two factors (columns) are further described in Table 1.

Two staging systems were excluded after the plenary discussion. Daly et al. (1972)¹⁴ did not describe the classifications or factors used. Coffin et al. (1983)²⁰ was excluded because of a lack of description of the stages.

The three most used factors in the existing classification and staging systems in the literature are objective factors, such as exposed bone and fistula, radiological factors, and pathological fractures (57.1%, 38%, and 52.4%, respectively). Two out of 21 studies (9.5%) described pain as a subjective factor in their classification. Nine (42.9%) classifications were treatment dependent. Six (28.6%) included a time factor. Four (19%) had positive radiological findings but did not specify the nature of these findings. Fourteen out of the 21 (66.7%) staging systems were only for one jaw, typically the mandible besides Cheng et al. (2006), which describes a staging system for the maxilla.

Discussion

Evaluating treatment outcomes and disease progression is difficult without a uniform internationally accepted classification and staging system. Over the last 30-40 years, several

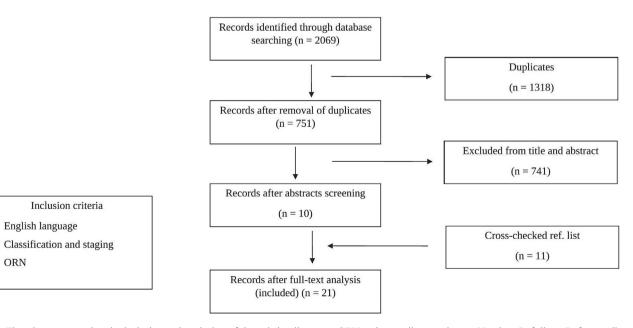


Fig. 1. Flowchart representing the inclusion and exclusion of the existing literature. ORN = Osteoradionecrosis, n = Number, Ref. list = Reference list.

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Table 1 Factors included in the existing classification and staging systems.

Author	Subjective factor		Objective factor			Radiological factor						Nonspecific finding	Cons
				Infection	Skin fistula/ oroantral/ oronasal fistula	pathological	•	Involvement of more than the alveolar bone	Involvement of the lower border (mandible)	Pathological fracture		A. Positive radiological finding B. Time factor C. Size on radiological and/or clinical examination D. Non-specific findings clinical	 Only one jaw Treatment-dependent
Støre ¹⁰		*	X	X	X	*						A	1
Schwartz ¹¹		*	X		X	*			X	X			1 + 2
Cheng ¹²		*	X	X		*					X	C	1
Baumann ²⁶		*	X			*							1 + 2
Karagozoglu ¹³	X	*	X		X	*			X			A + B	1
Lyons ¹⁸ He ¹⁹		*	X			*				X		C	1 + 2
He ¹⁹	X	*	X		X	*				X		C	1
Kanatas ³⁶		*			X	*	X	X		X			1
Daly ²⁰		*				*							
Marx ¹⁴		*	X			*				X			1 + 2
Coffin ²⁹		*				*				X		В	
Morton ²¹		*	X		X	*				X		В	2
Epstein ¹⁵		*				*				X		В	
Glanzmann ¹⁶		*	X	X		*						В	1 + 2
Clayman ¹⁷		*	X			*						A + D	2
Notani ²⁴		*			X	*	X	X		X			1
Chang ³⁸		*	X			*						A + B	1 + 2
Nabil ³³		*				*			X		X	A (A)	
Tsai ³²		*				*						(A)	1 + 2
Shaw ³⁴		*			X	*	X		X	X		C	

Table 1 summarises the factors relevant to the standardised classification of ORN. It also provides an overview of the factors included in the existing systems. The table shows that no staging system includes all the mentioned factors, and some systems incorporate only one or two factors. The 'non-specific findings' describe factors that cannot be categorised under the other headings.

- A: Positive radiological findings Non-specific description of changes on radiographs.
- B: Time factor Bone exposure for >3 months.
- C: Size (radiological and/or clinical): size of the clinically exposed or necrotic bone on radiographs.
- D: Non-specific findings Example: Clayman (1997): "A more aggressive type of ORN in which soft tissue breakdown occurs, exposing the bone to saliva and causing secondary contamination."

Asterisk (*) indicates that these two factors are not incorporated into any of the existing classification or staging systems.

Δ

classification systems have been proposed. Most studies relied on patient history, clinical progression of the disease, and/or response to treatment. This article presents an overview of the published ORN definitions and classification and staging systems for patients previously irradiated for head and neck cancers. However, none of these classification systems cover the complexity of the disease. Many authors have published ORN classifications, and most have relied on the clinical progression of the disease or its response to treatment.

Clinical presentation

There is large variability in the clinical presentation of ORN. Some patients are entirely asymptomatic, with no or only a small area of exposed intraoral bone. Other patients have extensive areas of exposed necrotic bone intraorally and/or extraorally, pathological fractures with intraoral and/or extraoral fistulae, and neurologic symptoms such as pain, dysesthesia, and/or anaesthesia.

Treatment

In the literature, the treatment of ORN varies, ranging from conservative therapy to minor and major surgeries. The choice depends on the general health of the patient and the extent of the ORN. Conservative treatment includes oral hygiene instruction, daily mouth rinsing with 0.2% chlorhexidine and antibiotics, if indicated. 6,8,9,11,12,14,15,21,22 Minor surgery is characterised by localised sequestrectomy and debridement of necrotic bone and granulation tissue, 8,12,21,22 whereas major surgeries refer to procedures such as block resection. In cases where necrosis extends to the base of the mandible or involves a pathological fracture, continuous resection is necessary. Subsequent reconstruction is performed when possible. ^{7,12,14,21,23} Marx et al. (1983)¹⁸ previously suggested the use of hyperbaric oxygen therapy as a supplement to the aforementioned treatment strategies. Systemic treatment with pentoxifylline and vitamin E has also been used to treat ORN.24

Definition

A precise and clear definition of a disease is paramount to any classification and staging systems. However, the definition of ORN varied among studies. The various definitions^{5,25} and proposals for the aetiology^{18,19} of ORN are considered relevant and capable of coexistence.

In the literature, the majority of authors seems to agree on the following points:

- 1. The affected area should be in the irradiation field. 6-8,10,26
- 2. Absence of recurrent malignancy in the affected area. 6,7,9,26
- 3. Soft tissue necrosis/breakdown with exposed underlying bone. 7,9-12,27

4. Necrosis of the exposed bone which has been irradiated. ^{7,8,28}

Factors to be discussed:

- The inclusion of a time factor, namely, the period of bone exposure.
- 2) The definition of necrotic bone.

Many authors have used time factors in their definitions. ^{7–12,27} Chrcanovic argued for the use of a time factor, ¹ but pointed out that it should not be too short or too long because of the risk of either over- or under-diagnosis. They proposed that, in the definition of ORN, bone exposure should be at least three months. However, ORN is a non-time-dependent disease. A diagnosis can be established as soon as a patient shows a probable bone, fistula, or exposed bone in a previously irradiated area.

The second factor is discussed as follows. The definition of necrotic bone varies, and it is difficult to define. Most authors conclude that when bone is exposed in an irradiated field without evidence of mucosal healing within a certain duration of time, then the bone is considered necrotic. ^{7–13,27} Støre et al. (2000)⁶ and He et al. (2015)²⁶ defined ORN and bone necrosis as changes on plain radiograph (X-ray). One must assume that exposed bone without mucosal coverage or healing is necrotic, but the exact diagnosis depends on histopathological examinations. ^{4,29}

Based on the discussion, the following modifications of the definition were made:

Probable or clinically exposed bone, with or without radiological evidence, in the irradiated area of the jaw (mandible or maxilla) where tumour recurrence has been excluded. Patients may present with symptoms such as pain and/or paraesthesia.

Classification/staging

Table 1 summarises the factors relevant to standardised classification and staging systems. The purpose of this table is to provide an overview of the factors included by different authors in existing classification and staging systems. As shown in Table 1, none of the existing staging systems incorporates all of the listed factors; some systems include only one or two. The category 'Non-specific findings' encompasses factors from existing systems that cannot be categorised under the other headings.

Some of the characteristics are discussed below:

- 1) Building a classification system for treatment strategies has been described in many existing systems in the literature. ^{7,8,10,12,15,23,27,30} If the treatment strategy is changed, the classification system is often unusable.
- 2) An ideal staging system should include a combination of subjective, objective, and radiological factors; that is, a prospective clinicoradiographic staging system for ORN. In the literature, only two authors have included subjective

- factors; ^{9,26} however, these were not defined. Two other authors included only objective factors, ^{12,23} and one included only radiological findings. ³¹
- 3) The incorporation of radiological factors into the classification of ORN requires the establishment of landmarks and an agreement on the type of radiological modality to be used. This approach facilitates the standardisation of ORN staging and classification.

In the literature, a distinguishing radiological factor is whether only the alveolar bone is involved or more than the alveolar bone. 21,32-34 Involvement of the bone above or below the alveolar canal,³³ reaching the lower border of the mandible^{7,9,31,32} or the occurrence of a pathological fracture has been described. 7,10,11,13,15,20–22,26,27,32–34 Another radiological landmark is the presence of dental pathological findings, such as apical or marginal pathology. Regarding medication-related osteonecrosis of the jaw - MRONJ Troeltzsch et al. (2023) demonstrated, through a large animal study, evidence of association between chronic oral infectious processes (periodontitis) and occurrence of MRONJ, even in the absence of any oral surgical procedure.³⁵ Only a few authors have incorporated radiographic findings into their classifications to provide information about the specific type of radiology used. Karagozoglu et al. (2014), Lyons et al. (2014) and Cheng et al. (2007) used orthopantomography. 9,27,36 Computed tomography (CT) is used by Cheng et al. (2007) and He et al. (2015). 26,36 A retrospective study made by Støre et al. (1999)³⁷ compared the value of CT scan with orthopantomography in the diagnosis and presurgical evaluation of mandibular ORN. They found that orthopantomography was suitable for monitoring mandibular ORN; however, but for diagnostic purposes or surgical intervention. Ogura et al. (2021) suggested that cone-beam CT (CBCT) could be useful for evaluating surgical specimens in patients with ORN, but mentioned that multimodal imaging techniques such as orthopantomography, scintigraphy, Magnetic Resonance Imaging (MRI) and CBCT are all useful for detecting ORN.²⁹

4) A classification system needs a stage that embraces the situation where the patients have no exposed bone but where subjective symptoms and radiological signs are present. In addition, there is a need for a stage called 'At Risk', as in the staging of MRONJ.³³ This stage included all patients who had received radiation therapy; however, no apparent necrotic bone or symptoms were observed. This stage also outlines treatment goals for patients with ORN.

In MRONJ, research has shown that exposed and non-exposed MRONJ could have similar radiological findings and subjective symptoms, but the only difference is the exposure of the bone.³⁸ The same may also apply to ORN. One scenario could be a patient with pain and radiological evidence of osteolysis, but no clinically exposed bone.

In the existing literature, Støre et al. (2000)⁶ suggested that stage 0 (denuded bone intraorally without any positive radiological signs) is a transient stage that may appear shortly after radiation therapy and from which spontaneous recovery may occur. He et al. described stage 0 as having no evident signs or only osteolytic images on radiography. However, the patients presented with typical ORN-related symptoms.²⁶ Cheng et al. (2007) also included a stage 0 in their classification but defined this as 'no ORN'.³⁶

There is a demand for a new classification and staging system that comprehensively addresses the complexity of ORN, enables the monitoring of disease progression,

Proposal for a new classification and staging system for osteoradionecrosis of the jaws.

	At risk Stage 0	Stage 2	Stage 3	
Symptom (subj.)	Pain (Yes or No)	Fain (Yes or No)	Pain (Yes or No) Sensory disturbances (Yes or No)	
Clinical finding (obj.)	All patients that Exposed bone or probable bone (No)	Acute infection (No) Exposed bone or probable bone (Yes)	Acute infection (Fes or No) Exposed bone or probable exposed bone (Fes) Acute infection (Fes) Cutaneous fistula (Fes) Ornantral(oronosal festula (Fes)	Ordinal/Ordinasai fistara (163)
Radiological finding (OTP, CT, CBCT)	All patients that received radiation therapy Apical and/or marginal pathology Involvement in only the alreador base	Involvement in only the alveolar bone	Involvement in <u>more</u> than the alveolar bone Pathological fracture (Yes) Involvement of the lower border of the mandible (Yes) Reaction in the maxillary sinus (Nec)	reaction in the maximaly sinus/involvement of the maximaly sinus (103)

Subj: = Subjective, Obj: = Objective, OTP = Orthopantomography, CT = Computed Tomography, CBCT = Cone-Beam CT

assesses treatment outcomes, and allows for the comparison of treatment regimens. Table 2 presents our proposed classification and staging system designed to fulfil these requirements.

Our group internally evaluated the reproducibility of our classification and staging system. Ten consecutive patients with ORN from our clinic were retrospectively reviewed and staged by each author, as shown in Table 2. These cases are discussed in a preliminary session. There was predominant agreement (80%), with disagreements occurring in only two cases.

In the near future, we aim to test the functionality of the proposed classification and staging system in our clinic and between different Oral and Maxillofacial departments in Scandinavia. All patients referred to our department with ORN should be staged according to our new classification system. Patients who have undergone radiotherapy for head and neck cancer are initially classified as 'At Risk.' Those who progress to a severe stage are documented, and an appropriate treatment plan is implemented. Following treatment, patients are restaged to assess whether ORN has improved, worsened, or remained stable. This system facilitates treatment evaluation, supports clinical decision-making, and allows patient outcomes to be monitored and compared both locally and internationally.

Conclusion

None of the existing classification systems covers the complexities and nuances of ORN.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patient permission

Not required.

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