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Osteoradionecrosis of the mandible: A ten year single-center retrospective study



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ABSTRACT

Background: Numerous factors have been associated with the development of osteoradionecrosis (ORN) of the jaws. The purpose of this study was to investigate the factors that are linked to the severity of mandibular ORN.

Methods: A retrospective study was conducted which included all ORN cases treated in the Department of Oral and Maxillofacial Surgery in Munich (LMU) between 2003 and 2012. The cases were categorized according to the necrosis stage and several variables were evaluated in order to identify possible correlation between them and the severity of the necrosis.

Results: A total of 115 patients with 153 osteonecrosis lesions were included in the study. Twenty-three cases were of stage I, 31 were of stage II and 99 were of stage III. The initial tumors were predominantly located in the floor of the mouth, the tongue or the pharynx. Diabetes mellitus (OR: 4.955, 95% CI: 1.965–12.495), active smoking (OR: 13.542, 95% CI: 2.085–87.947), excessive alcohol consumption (OR: 5.428, 95% CI: 1.622–18.171) and dental treatment and/or local pathological conditions (OR: 0.237, 95% CI: 0.086–0.655) were significant predictors for stage III necrosis.

Conclusions: The aforementioned factors are predictive of ORN severity and can guide its prophylaxis and management.

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1. Introduction

Osteoradionecrosis (ORN) is a devastating complication of radiotherapy (RT) in head and neck cancer. 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 tumor (Marx, 1983a, Marx and Johnson, 1987, Teng and Futran, 2005, Pitak-Arnnop et al., 2008). Although the pathogenesis mechanism is still under investigation, the most frequently reported reason is radiation arteritis, which leads to the development of a hypocellular, hypovascular, and hypoxic environment (Marx, 1983b, Fenner et al., 2010).

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The average age of patients with ORN is over 55 years (Reuther et al., 2003, Pitak-Arnnop et al., 2008, Almazrooa and Woo, 2009). Mandibular ORN predominates when compared with maxillary ORN (ratio mandible: maxilla is approximately 24:1) (Perrier and Moeller, 1994). In previous studies, the incidence of ORN in a population that has received head and neck irradiation was estimated to be 4.74–37.5% (Murray et al., 1980a, Morrish et al., 1981, Epstein et al., 1987a, Reuther et al., 2003). Recent studies have shown an incidence decreased to lower than 5% and have attributed the phenomenon to improved dental preventive care and improved radiation techniques, such as 3-dimensional conformal RT (3D-CRT) and intensity-modulated RT (IMRT) (Jereczek-Fossa and Orecchia, 2002, Reuther et al., 2003, Studer et al., 2004).

Numerous factors have been associated with the risk of ORN development (Morrish et al., 1981, Kluth et al., 1988, Jereczek-Fossa and Orecchia, 2002, Reuther et al., 2003, Niewald et al., 2013). They can be divided into three main groups (Jereczek-Fossa and Orecchia, 2002):

1. Tumor-related factors (size and stage of tumor, anatomic tumor site, proximity of tumor to bone).
2. Treatment-related factors (total dose, photon energy, brachytherapy, field size, fraction size, volume of the mandible irradiated).
3. Patient-related factors (periodontitis, pre-irradiation bone surgery, poor oral hygiene, alcohol and tobacco abuse, bone inflammation, dental extraction after RT).

Some of these factors are related to a high risk of developing ORN; others account for a lower risk depending on the population under investigation and other parameters.

Until now, many studies have investigated the entity of ORN as well as the risk factors associated with its occurrence and several staging systems have been proposed to aid its management. A comprehensive search of the literature (PubMed and MEDLINE Database, Cochrane Library) revealed a distinct lack of studies aiming to identify factors associated with the severity of mandibular ORN. Its investigation is clinically extremely important since the management of severe cases differs considerably from that of early-stage disease. Clinical symptoms, radiological findings and prophylaxis protocols also present a wide variance among the different stages of necrosis.

For these reasons, the purposes of this study are to:

- i) describe the demographic data of the patients that were treated for ORN, ii) examine the tumor characteristics, oral status and symptomatology of the affected patients, iii) examine ORN distribution in the oral cavity, iv) record the treatment methods provided, and finally v) identify risk factors associated with the severity of ORN.

2. Material and methods

A retrospective analysis was conducted of 115 patients who were diagnosed with ORN and were treated in the Department of Oral and Maxillofacial Surgery in Munich (LMU) in the period from January 2003 to December 2012. These patients suffered from ORN on one or more occasions, with the second outbreak being independent from the initial occurrence and not an exacerbation of the latter. The study was approved by the Ethical Committee of the University of Munich (Project-Nr. 083-11).

Inclusion criteria were the following:

- Patients with head and neck tumors who had been treated with surgery and/or RT and/or chemotherapy one or more times in their life,
- Patients with denuded bone in the oral cavity for a period of more than 3 months,
- Patients with no evidence of persisting or recurrent tumor,
- Patients with no use of antiresorptive drugs (bisphosphonates or denosumab) before, during or after tumor therapy,
- Patients with histologically proven ORN.

Data were gathered by searching the medical records of the patients including files, letters, radiographic findings, histological examinations, photographs and operational reports. The data that were collected included:

1. Personal data (age, sex),
2. Health data (general health problems, smoking, alcohol consumption),
3. Tumor data (localization, staging, means of therapy, dose of radiation, times of radiation),
4. Oral health data (dental examination and treatment before, during or after RT),

5. Information on symptomatology and factors that contributed to the onset of ORN,
6. Information on the methods of treatment provided to these patients,
7. Information on the exact localization of necrosis in the jaws.

All radiological examinations (OPT, CT, MRI) were thoroughly examined not only for general pathologic changes but also for abnormalities specific to ORN lesions. These included localized osteolytic areas, extensive osteolytic areas, sequestra, fractures, persistent sockets after tooth extraction and mixed radio-opaque radiolucent lesions.

Particular emphasis was given to the exact localization of necrosis. Localization was recorded after search in the medical files and was compared with the available data on radiological examinations and photos. The affected regions were numbered according to the International Dental Scheme of Fédération Dentaire Internationale (FDI). A distinction between localization in the maxilla and mandible was also conducted.

RT was categorized as RT in the head and neck region or RT in other parts of the body; metastasis in bone was differentiated from metastasis in other parts of the body. Smoking was recorded not only for active smokers at the time of the study but also for those who had given up smoking after tumor therapy. The alcohol consumption was referred to as positive when the patient was drinking more than the amount determined by the American Heart Association as normal consumption. Normal alcohol consumption is an average of one to two drinks per day for men and one drink per day for women. A drink is defined as one 12 oz. beer, 4 oz. of wine, 1.5 oz. of 80-proof spirits, or 1 oz. of 100-proof spirits (American Heart Association 2014).

Tumors were categorized in stages, according to the TNM classification, which was developed and maintained by the Union Internationale Contre le Cancer (UICC). Tumors were divided in two groups according to their connection with the adjacent tissues (soft and hard tissues) and into four groups according to their localization (maxilla, mandible, oropharynx, other).

Triggers of ORN included extraction of a tooth, root canal treatment, denture irritation, implantation, marginal or apical periodontitis and impacted wisdom tooth. For better analysis, these variables were divided into two groups in the present study. The first group included dental procedures such as extraction, implantation and extraction combined with other dental treatment. The second group included local pathological conditions such as denture irritation, marginal periodontitis, impacted wisdom tooth and apical periodontitis. Apart from these two groups, there was a special category for the ORN cases that occurred spontaneously.

The following symptoms were documented: exposure of bone, pain, swelling, inflammation, fistula, fracture, pus and inferior alveolar nerve hypesthesia. The treatment provided was divided into two groups: i) conservative including antibiotics, analgesics and hyperbaric oxygen (HBO) therapy, and ii) surgical including debridement, radical sequestrectomy, alveolectomy with primary closure or hemimandibulectomy, closure of orocutaneous fistulae and local or microvascular free flap reconstruction.

Initially, the descriptive assessment of the data was carried out by calculating the observed values and the relative frequencies over the entire patient population. Then, the total sample was categorized in three groups (stages) based on the classification of [Notani et al., 2003 \(Table 1\)](#).

The variables were analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics v.22, New York, NY, USA). Data analysis included descriptive statistics by analyzing the observed values and the frequencies. The association between categorical variables was tested for statistical significance using the chi-square

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