



Retrospective study of osteoradionecrosis in the jaws of patients with head and neck cancer

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Abstract (J Korean Assoc Oral Maxillofac Surg 2019;45:21-28)

Objectives: Osteoradionecrosis (ORN) is one of the most severe complications resulting from radiotherapy (RT) in patients with head and neck cancer (HNC). It is characterized by persistent exposed and devitalized bone without proper healing for greater than 6 months after a high dose of radiation in the area. To describe the profile and dental management of ORN in HNC patients undergoing RT in an oncological clinical research center.

Materials and Methods: A retrospective descriptive study was performed to analyze dental records from HNC patients with ORN treated at an oncological clinical research center from 2013 to 2017. A total of 158 dental records for HNC patients were selected from a total of 583 records. Afterwards, this number was distributed to three examiners for manual assessments. Each examiner was responsible for selecting dental records that contained an ORN description, resulting in 20 dental records.

Results: Mean patient age was 60.3 years with males being the most affected sex (80.0%). The most affected area was the posterior region of the mandible (60.0%) followed by the anterior region of the mandible (20.0%) and the posterior region of the maxilla (10.0%). The factors most associated with ORN were dental conditions (70.0%) followed by isolated systemic factors (10.0%) and tumor resection (5.0%). There was total exposed bone closure in 50.0% of cases. The predominant treatment was curettage associated with chlorhexidine 0.12% irrigation (36.0%).

Conclusion: Poor dental conditions were related to ORN occurrence. ORN management through less invasive therapies was effective for the closure of exposed bone areas and avoidance of infection.

Key words: Osteoradionecrosis, Head and neck neoplasms, Mandible, Conservative treatment, Maxilla

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I. Introduction

Osteoradionecrosis (ORN) is one of the most severe complications resulting from radiotherapy (RT) in patients with head and neck cancer (HNC) and can occur between four to twenty-four months after RT¹. In the literature, there are several definitions for ORN that are based mainly on clinical findings when, after head and neck radiation, the bone becomes exposed and devitalized, persisting without proper

repair for a 3 to 6 month period, resulting in ORN²⁻⁴. Firstly described by Regaud⁵ in 1922, ORN involves a combination of four factors: radiation, hypoxia, hypovascularization, and hypocellularization resulting in bone necrosis. The mandible is the most affected bone in head and neck radiation patients⁶⁻⁸.

ORN can occur spontaneously or due to local factors including tumor localization, dose and/or type of RT⁹, trauma due to dental prosthetics, dental surgeries before, during, or after RT, deficient oral hygiene, and local infections including periodontal disease and dentoalveolar abscesses⁹⁻¹². Arteriopathies, diabetes, alcoholism, and malnutrition are systemic factors that contribute to ORN¹³. The diagnosis of this complication is based on clinical characteristics including bone exposure, infection, halitosis, fistula, pathological fracture, and local pain¹⁴. In asymptomatic cases, ORN can be presumptively diagnosed with radiographic exams¹⁵.

Once the cause of ORN is determined, various types of treatment can be employed, including irrigation with

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chlorhexidine 0.12%, use of antibiotics, and surgical intervention^{1,16,17}. Surgical resection and hyperbaric oxygen therapy (HOT) have been reported to be therapies of choice¹⁸, although perhaps the maximum benefit is obtained through a combination of various therapy strategies^{1,16,17}. Currently there is no gold standard treatment for ORN nor widely accepted guidelines. Early diagnosis and oral condition monitoring are crucial for the prevention and successful treatment of ORN¹⁶.

Considering how few studies have evaluated the conduct of clinical protocols for ORN, the present study aimed to describe the profile and dental management of ORN in patients undergoing head and neck RT in an oncological clinical research center.

II. Materials and Methods

A retrospective descriptive study was performed using dental record data of patients with ORN treated in an oncological clinical research center. At first, a search was performed in the electronic registration system containing 583 dental records of all the treated patients. Afterwards, HNC patients were selected, totaling 158 records which were distributed to three examiners for manual assessment. Each examiner was then responsible for selecting dental records that contained a description of ORN, resulting in a final total of 20 dental records.(Fig. 1)

From the 20 dental records of patients with ORN, information was collected regarding their age, sex, type and/or HNC localization, cancer stage, type of treatment, dose, and RT type. Regarding ORN, the localization, time between the last dental appointment and first description of ORN, predisposing factors for ORN, type of treatments administered, and outcomes between the first and last description of ORN were considered. In addition, ORN cases were classified according to the Støre and Boysen¹⁸ score based on clinical characteristics described in the dental records. Following this score, isolated mucosal defects were classified as stage 0 (zero); cases with radiological evidence of necrotic bone with intact mucosa were classified as stage I; cases with exposed bone and radiological evidence were classified as stage II; and cases with exposed bone, radiological evidence, extraoral fistula, and infection were classified as stage III. All patients signed the informed consent form in accordance with the Declaration of Helsinki.

III. Results

In a 4 year period (2013-2017), 158 individuals with HNC were treated at the Clinical Research Center of Bauru School of Dentistry, University of São Paulo (Bauru, Brazil). One hundred thirty-nine patients (88.0%) received RT in the head and neck region and 20 of them were diagnosed with ORN. Sixteen patients (80.0%) with ORN were male and 4 patients (20.0%) were female. The mean age was 60.3 years with a range from 29 to 85 years.(Table 1)

The most common types of cancer in patients who underwent head and neck RT were oropharyngeal (38.1%) and oral (31.7%) cancers.(Table 2) There was a higher incidence of ORN in individuals with squamous cell carcinoma (SCC) on the floor of the mouth at 70.0% followed by the alveolar ridge SCC with 50.0% of cases in patients with oral cancer. Patients with oral and oropharyngeal cancers developed ORN 50.0% of the time.(Table 3)

Related to antineoplastic treatment modalities, of the 11 patients who underwent only RT, 6 developed ORN; of the 32 patients who underwent RT associated with chemotherapy and surgery, 6 developed ORN; of the 28 patients who underwent RT associated with surgery, 4 developed ORN; and of the 60 patients who underwent RT and chemotherapy, 4 developed ORN. The majority of ORN cases occurred in individuals who underwent conventional/cobalt RT (10 cases).

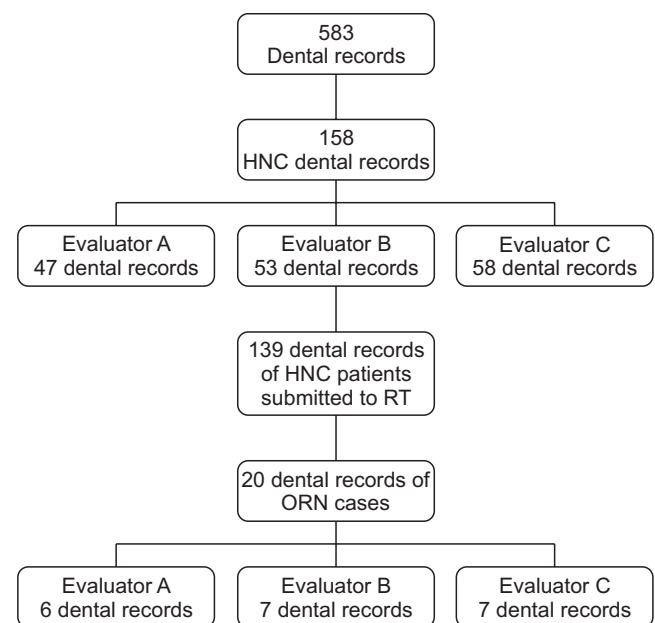


Fig. 1. Flow chart of study design. (HNC: head and neck cancer, RT: radiotherapy, ORN: osteoradionecrosis)
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Table 1. Distribution of HNC patients with ORN including epidemiology and treatment type

Age (yr)	Sex	Type of cancer	Cancer staging	Treatment	Dose (cGy)/type of RT	ORN localization	Begin-ning of ORN	Stage of ORN	Predisposing local factors	ORN treatment	ORN outcomes
55	M	Mouthfloor SCC	T4N0M0	CT+RT	7,020/cobalt	Posterior region of right mandible	49 mo	2	Dental extraction, smoking	Curettage+chlorhexidine 0.12% irrigation	Absence after 15 mo
80	M	Mouthfloor SCC	-	RT	6,840/cobalt	Posterior region of mandible	6 mo	2	Unsatisfactory FP, smoking, alcoholism	Curettage+chlorhexidine 0.12% irrigation	Presence ¹
58	M	Nasopharynx SCC	TxN2bM0	RT	5,580/cobalt	Anterior region of mandible	5 mo	2	Dentoalveolar abscess	Curettage+chlorhexidine 0.12% irrigation	Absence after 7 mo
60	M	Mouthfloor SCC	T4N0M0	RT	7,000/IMRT	Posterior region of mandible	6 mo	2	Dental extraction	Curettage+chlorhexidine 0.12% irrigation	Presence ¹
52	M	Mouthfloor SCC	T2N2cM0	RT	6,000/IMRT	Posterior region of left mandible	8 mo	2	Dental extraction, smoking	Curettage+chlorhexidine 0.12% irrigation	Presence ¹
73	M	Mouthfloor SCC	-	RT	7,000/IMRT	Posterior region of right mandible	2 mo	2	Dental extraction, smoking	Curettage+chlorhexidine 0.12% irrigation+ ozone therapy	Absence after 13 mo
60	M	Alveolar ridge SCC	TisN0M0	RT	6,000/IMRT	Posterior region of left mandible	7 mo	2	Alcoholism	Curettage+chlorhexidine 0.12% irrigation	Absence after 6 mo
66	F	Mouthfloor SCC	-	Surgery+RT	6,400/IMRT	Anterior region of mandible	Same month	3	Tumor resection	Curettage+chlorhexidine 0.12% irrigation+ osteoplasty+ATB+mandibulectomy	Absence after 13 mo
85	F	Buccal mucosa SCC	-	Surgery+RT	6,480/cobalt	Anterior region of mandible	16 mo	2	Unsatisfactory FP	Chlorhexidine 0.12% hygiene+bone fragment removal+ostectomy	Absence after 7 days
49	M	Oropharynx SCC (tongue basis and tonsillary pillar)	-	CT+RT+surgery	6,480/cobalt	Right mandible	18 mo	2	-	Curettage+chlorhexidine 0.12% irrigation+ ozone therapy	Presence
74	M	Oropharynx SCC	T4N2bM0	RT+CT	-	Posterior region of left mandible	17 mo	3	Dental extraction	Curettage+chlorhexidine 0.12% irrigation+ATB	Presence
49	M	Tongue basis SCC and retromolar area	T2N1M0	Surgery+CT+RT	6,400/cobalt	Posterior region of right mandible	1 mo	2	Dental extraction, smoking	Curettage+chlorhexidine 0.12% irrigation	Presence
61	M	Mouthfloor SCC, tongue basis, and oropharynx	T2N0M0	CT+ RT+surgery	6,600/cobalt	Anterior region of mandible to left posterior region	2 mo	3	Smoking	Curettage+ chlorhexidine 0.12% irrigation+ sequestratomy+ATB	Presence on anterior region of mandible
63	M	Oropharynx SCC (left tongue basis)	-	CT+RT+surgery	6,840/IMRT	Left mandible	11 mo	3	Unsatisfactory PRP, smoking	Chlorhexidine 0.12% hygiene+ATB+HOT+ pentoxiphiline+vitamine E	Absence on posterior region after 1 mo
											Presence

Table 1. Continued

Age (yr)	Sex	Type of cancer	Cancer staging	Treatment	Dose (cGy)/type of RT	ORN localization	Begin- Stage of ORN	Predisposing local factors	ORN treatment	ORN outcomes
63	F	Right face skin SCC	-	RT+surgery	5,040/cobalt	Right maxilla Anterior region of maxilla	9 mo 2	-	Curettage+chlorhexidine 0.12% irrigation	Absence after 2 mo
47	F	Left buccal mucosa SCC	T3N0M0	Surgery+RT	6,000/IMRT	Posterior region of left maxilla	3 days 2	Periodontal disease	Curettage+chlorhexidine 0.12% irrigation+ sequestratomy	Absence after 10 days
29	M	Palate adenocarcinoma	T3N0M0	Surgery+RT+CT	6,000/IMRT (tumor area) 5,400/IMRT (cervical region)	Posterior region of right maxilla	2 mo 2	-	Curettage+chlorhexidine 0.12% irrigation+ sequestratomy	Absence after 3 mo
66	M	Oropharynx SCC	T2N2M	RT+CT	5,000-7,000/cobalt	Right mandible Posterior region of left mandible	15 mo 3	Residual root, dentoalveolar abscess, alcoholism	Curettage+chlorhexidine 0.12% irrigation+ATB	Absence after 4 mo
61	M	Oropharynx SCC (uvula)	-	RT+CT	6,300/cobalt	Posterior region of right mandible	10 mo 2	Dental extraction	Curettage+chlorhexidine 0.12% irrigation	Presence
63	M	Left mouthfloor SCC	T4aN2bM0	RT+CT+surgery	7,000/3D-CRT	Left mandible	2 mo 3	Dental extraction, periodontal disease, smoking, tumor	Curettage+chlorhexidine 0.12% irrigation+ATB	Presence ¹

(HNC: head and neck cancer, ORN: osteoradionecrosis, M: male, F: female, SCC: squamous cell carcinoma, -: not informed, CT: chemotherapy, RT: radiotherapy, IMRT: intensive modulated radiotherapy, FP: full prosthesis, PRP: partial removable prosthesis, ATB: antibiotics, HOT: hyperbaric oxygen therapy, 3D-CRT: 3-dimensional conformal radiation therapy)
¹Death.

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Table 2. Tumor sites in 139 patients irradiated in the head and neck area

Site	Value
Oropharynx	53 (38.1)
Oral cavity	44 (31.7)
Larynx	20 (14.4)
Hypopharynx	4 (2.9)
Nasopharynx	8 (5.8)
Others ¹	12 (8.6)

¹Tumors of the parotid, maxillary sinus, skin, brain, thyroid, and hypophysis.

Values are presented as number (%).

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Table 3. Incidence of ORN in irradiated HCN according to tumor location

Primary tumor	Value
Oral cancer (n=11)	
Mouthfloor SCC	7/10 (70.0)
Alveolar ridge SCC	1/2 (50.0)
Buccal mucosa SCC	2/7 (28.6)
Palate adenocarcinoma	1/9 (11.1)
Skin SCC	1/1 (100)
Oral cancer+oropharynx cancer	2/4 (50.0)
Nasopharynx cancer	1/8 (12.5)
Oropharynx	5/48 (10.4)

(ORN: osteoradionecrosis, HCN: head and neck cancer, SCC: squamous cell carcinoma)

Values are presented as number (ORN/total tumors) (%).

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The type of RT was not reported in 18 patients who underwent RT in the head and neck region, and only one of these cases presented with ORN.(Table 4) The dose of RT varied between 5,000 cGy and 7,020 cGy.(Table 1)

The most common ORN site was the posterior region of the mandible, with 12 individuals (60.0%), followed by the anterior region of the mandible with 4 cases (20.0%), posterior maxilla with 2 cases (10.0%), 1 case (5.0%) in the anterior to posterior maxilla, and 1 case (5.0%) that affected the anterior and posterior regions of the mandible. Regarding ORN stage, 14 out of the 20 (70.0%) cases were classified as stage 2 and 6 out of the 20 cases (30.0%) were classified as stage 3.(Table 1)

Among the ORN predisposing factors, 14 cases (70.0%) were related to dental conditions (dental extractions, dentoalveolar abscesses, periodontal disease, dental prosthetics, and residual roots), 2 cases (10.0%) were associated with systemic factors (tobacco and alcohol use), 1 case (5.0%) was associated with surgery for tumor removal, and it was not possible to find descriptions of associated predisposing factors in 3 cases (15.0%). Dental extractions and tobacco use

Table 4. Incidence of ORN according to antineoplastic treatment

Radiotherapy	Value
Modality	
RT	6/11 (54.5)
RT+CT+surgery	6/32 (18.8)
RT+surgery	4/28 (14.3)
RT+CT	4/60 (6.7)
Type of RT	
Cobalt/conventional	10/54 (18.5)
IMRT	8/53 (15.1)
3D-CRT	1/14 (7.1)
Not informed	1/18 (5.6)

(ORN: osteoradionecrosis, RT: radiotherapy, CT: chemotherapy, IMRT: intensive modulated radiotherapy, 3D-CRT: three-dimensional conformal radiation therapy)

Values are presented as number (ORN/antineoplastic treatment) (%).

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were present in 8 cases (40.0%), followed by badly adapted prosthetics and alcohol use in 3 cases (15.0%), and residual roots, dentoalveolar abscesses, and dehiscences following tumor removal in 1 case (5.0%) each. ORN minimal clinical presentation time was immediate in 2 cases (10.0%), and the larger clinical presentation time after RT totaled 49 months with an average of 6.5 months. Half of the ORN cases (50.0%) were diagnosed 6 months after RT and after 2 months for 4 cases (20.0%).(Table 1)

Many different approaches were used for ORN treatment with the most frequent ones involving curettage and 0.12% chlorhexidine irrigation in 9 cases (45.0%), 2 cases (10.0%) of sequestrectomy associated with curettage and 0.12% chlorhexidine irrigation, and 2 cases (10.0%) of curettage associated with 0.12% chlorhexidine irrigation and antibiotic therapy. The other associated treatment modalities (1 per case) are presented in Table 1.

ORN outcomes included 10 cases (50.0%) that resulted in closure of the exposed bone and in 1 case (5.0%) presenting in the anterior and posterior regions of the mandible, there was only posterior region closure. In 4 cases (36.0%) where there was bone exposure closure/epithelialization, the treatment modality used was curettage associated with 0.12% chlorhexidine irrigation.(Table 1) The other closure cases encompassed several treatment types aforementioned.

IV. Discussion

In the present study, ORN was found more often in elderly (61-85 years) males (80.0%) with an average age of 60.6 years; a little older than findings from previous studies^{19,20} (54.0²¹, 55.2²², and 57.8¹⁹ years). ORN was commonly found

in patients with SCC on the floor of the mouth (70.0%) in our study^{9,22}.

Complications resulting from RT are more frequent in irradiated regions, resulting in ORN risk factors based on RT type and radiation dose. Therapy with intensive modulated radiotherapy (IMRT) presents an advantage in ORN prevention, since the ORN rate with IMRT (4%) is lower compared to three-dimensional (3D) conformal radiation therapy (3D-CRT) (19%)²²⁻²⁶. In this study, most individuals with ORN underwent conventional RT (18.5%) and IMRT (15.1%) with only 1 case (7.1%) receiving 3D-CRT.(Table 4) Doses higher than 5,000 cGy also raise the risk of ORN, with greater risk seen in doses higher than 6,000 cGy^{27,28}. ORN occurred in irradiated fields with doses ranging from 5,000 to 7,020 cGy with more frequent total doses of 6,000 cGy (4/20) and 7,000 cGy (4/20). ORN occurred independent of the treatment modality (RT and/or CT and/or surgery) and conveyed the fact that higher radiation doses contributed significantly to ORN.

When ORN occurs in the context of dental conditions associated with systemic factors (e.g., tobacco and alcohol use), including dental extractions, infections or abscesses, and trauma caused by dental prosthetics in the irradiated field, there is an increased risk for ORN^{24,29-32} even though ORN can occur spontaneously. In this study, ORN was found more frequently in the mandible (80.0%), which is the region adjacent to the location of most tumors (oral floor, tongue, and retromolar trigone region), but was also present in the maxilla (10.0%), localized next to tumors. These regions supposedly received direct radiation in high doses, seemingly the determinant factor for ORN in this study. The concept of bone density differences and blood supply between the maxilla and mandible becomes secondary.

Most ORN cases in this study were related to dental conditions (70.0%) with only 2 cases (10.0%) not being related to local predisposing factors, where ORN could have possibly occurred spontaneously which would be contrary to previous studies in which 79%²³ and 82%³³ of the ORN cases occurred spontaneously. Among the dental conditions, dental extractions and tobacco use were the predisposing factors more often associated (40.0%) with ORN, followed by trauma and alcohol use (15.0%). In another study, a low ORN rate (1.7%) related to dental extractions was found²³. However, the association with tobacco and alcohol use increased ORN risk and severity^{27,22}. The time for ORN development after the end of RT was usually within 3 years, and varied from 0 months to 192 months in cases of chronic trauma^{9,34}. In this study, half (50.0%) of the ORN cases occurred 6 months after the end of

RT and ranged between 0 to 49 months with an average (6.5 years) below the one found in previous studies (8 months)^{21,22}.

Challenges for daily clinical assessments include case identification, pain source, and differentiation of ORN clinical signs when it is still in its initial stages from other side effects resulting from SCC treatment that can affect the oral mucosa, including oral mucositis²³. Furthermore, it is difficult to identify radiographic alteration signs for ORN since they are only detectable when 30% to 40% of the bone density is compromised^{18,35}. These facts can explain the lack of description in the medical records of this study as well as signs of ORN initial stages (0 or 1), thus making it impossible to perform ORN retrospective ratings for stages other than stages 2 (70.0%) and 3 (30.0%) which had clinical sign descriptions.

ORN treatment is difficult, involves a combination of therapies, depends on available therapeutic resources, and relies on patient compliance with instructions and their individual biological response. For many researchers, conservative treatment is performed only in small ORN areas since for more advanced conditions, surgical resection is considered more efficient¹. The conservative and surgical approach associated with HOT is well documented^{1,19,36}. A less invasive option for ORN control and healing involves 0.12% chlorhexidine which, when administered topically, acts as a bactericide against gram-positive and gram-negative microorganisms and some yeasts. Despite exhibiting good results when associated with superficial necrotic bone curettage, there is still no protocol for the use of chlorhexidine for ORN treatment^{1,17}.

Less invasive treatment options were the first choice for ORN cases in this study. Even for more advanced cases, 0.12% chlorhexidine irrigation was administered. For all stage 3 ORN cases, the use of an associated systemic antimicrobial was introduced based on the presence of local suppuration. There was epithelialization in 8 (57%) stage 2 ORN cases and in 2 (33%) stage 3 ORN cases. In one case, there was total ORN resolution due to surgical resection. Bone exposition closure was observed in most cases (11/20) in this study which were treated with less invasive therapies.

V. Conclusion

Dental extractions, dentoalveolar abscesses, and ill-fitting dental prosthetics in directly radiated regions predisposed the areas to ORN. ORN management through less invasive therapies was effective for the treatment and control of ORN.

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Authors' Contributions

B.R.M., M.A.O., and N.G.S. participated in data collection and wrote the manuscript. P.S.S.S. participated in the study design and coordination. B.R.M. and N.G.S. performed the statistical analysis. C.M.F.R. helped to draft the manuscript. All authors read and approved the final manuscript.

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Ethics Approval and Consent to Participate

This study was a retrospective study with only archived records and as stated in the standards set forth in the instruction manual for submitting this journal, only experimental studies need the approval of the Institutional Review Board (IRB). Therefore, it can be justify the exemption of IRB approval for this study.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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