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Risk factors for jaw osteoradionecrosis: a case control study

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Abstract: There are divergences among studies regarding features associated to increased risk of osteoradionecrosis (ORN). Our objective was to identify factors that predispose to the development of ORN of the jaw. This was a retrospective, hospital-based, case-control study involving patients with head and neck cancer who had been treated with ≥ 60 Gy external radiotherapy (RT) to the jaw. A total of 19 cases of ORN and 43 controls were included. The patients' demographic data, tumor type, staging, treatment and outcome information, and pre-treatment oral status were collected. Univariate analysis showed that the oral cavity/oropharynx sites were associated with 9.77-fold increased risk of ORN development compared to other sites (p = 0.005). Being an active smoker was associated with 3.95-fold increased risk of ORN development (p = 0.01). A tendency towards increased risk of ORN was observed particularly when tooth extraction occurred after RT (odds ratio (OR): 3.04; p = 0.08). Multivariable analysis showed that tumor site was the only significant risk factor (OR: 21.03, p = 0.01). The oral and oropharyngeal primary site is an important risk factor for ORN. Dental extraction, which did not occur in 28% of the sample, was not an essential event for ORN development.

Keywords: Risk Factors; Osteoradionecrosis; Case-Control Studies; Mouth Neoplasms.

Introduction

In radiotherapy of head and neck cancers, the proximity of the target volumes to important anatomic structures poses the risk of toxicity, which is a consequence of trying to achieve the best local or regional control. Even though the lower jaw is in general a radioresistant structure, it is the craniofacial bone that is most commonly associated with osteoradionecrosis (ORN) in head and neck oncology, especially when exposed to doses higher than 60 Gy.[1] The incidence varies, ranging between 10 and 15% in recent publications.[2] One of the last published systematic reviews found an overall risk of 2% for patients who undergo radiotherapy for head and neck cancer, but certain subpopulations have a higher risk, such as those who undergo post-irradiation tooth extraction (6.88%).[3] Various definitions of ORN have been proposed, with one of the most widely accepted being exposed bone after radiotherapy that fails to heal over a period of 3–6 months, without evidence of persistent or recurrent tumor.[4,5] ORN may

lead to a pronounced reduction in quality of life, which can lead to pain, fractures, sequestration of devitalized bone, and fistulas.[6]

Poor vascularization of the lower jaw is the most probable reason the mandible is the most common location for ORN. In the upper jaw, ORN develops less progressively and the defects are less severe.[7] Bone exposure, fractures, inflammation, and wound healing disorders are the most commonly reported symptoms.[8] Despite many controversies around ORN pathophysiology, recent advances in cellular and microbiology have allowed the development of the radiation-induced fibroatrophic theory. This theory states that the key event in the progression of ORN is the activation and deregulation of fibroblastic activity, leading to atrophic tissue. The hypothesis focuses on defective radiated bone and the imbalance between tissue synthesis and degradation in a prefibrotic and a late fibroatrophic phase. During the late fibroatrophic healing phase, tissues are vulnerable to reactivated inflammation in the event of local injury. The result is hypocellular bone and reduced bone matrix formation compensated by fibrosis.[9]

Many variables have been associated with the development of ORN, such as smoking, dental hygiene, alcohol consumption, various comorbidities, and treatment-related factors, including dental extractions and their temporal relation to radiotherapy protocols, in addition to dose-volume correlations of the irradiated mandible.[10] Although there are some divergences among studies, the evidence points to a consensus about the association of higher radiation doses, smoking (especially current smoking), and post-radiotherapy exodontia with a higher risk of ORN.[11-13] Patients who continued to smoke during radiation treatment had 32% increased risk of developing ORN and 46% increased risk of requiring hospitalization during treatment compared with those who quit smoking while undergoing radiation therapy.[14]

Given the relatively low incidence of ORN, the number of ORN cases included in the published literature is small. Some studies show similar results between dental extractions before and after radiotherapy. In general, the decision to extract teeth before or after irradiation treatment has not traditionally been based on evidence from studies. Despite the extensive literature on ORN, there is evidence of consistent risk for only a fraction of the factors examined. Furthermore, many of the publications are case reports, case series with no disease-free controls, small sample sizes, and cohorts with short follow-up periods for controls.

The main purpose of the present study was to identify and assess the factors that predispose to the development of ORN through a case-control study. Identifying the predictive factors would allow the identification of patients at greater risk of developing ORN. Appropriate measures can then be put in place both to reduce the risk of developing ORN and expedite management in the event of its occurrence.

Methods

Selection of cases and controls

This study was conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki. Following Institutional Review Board approval (4.087.868), we selected ORN cases from our hospital data system that met the following criteria: patients being followed by the head and neck team of our institution who had been identified with ORN of the jaw after being treated for head and neck malignant neoplasia between January 2010 and December 2020. Cases were selected by filtering for CID M87 and its variants and reviewing the totality of pathology reports of the department's surgeons, reports of surgical procedures performed by the head and neck department, reports of follow-up patients after surgeries performed by any surgeon in the department, and reports of outpatient consultations performed by the department's public health system. A sample of 21 potential cases was initially selected. Those with mandibular necrosis owing to tumor destruction and multiple treatments (one case) and those lost to follow-up after diagnosis of ORN (one case) were excluded. Use of bisphosphonate treatment also was considered an exclusion criterion (no cases). Nineteen cases were included in the statistical analysis.

The controls were selected by filtering a consecutive series of patients with a diagnosis of

head and neck cancer who had undergone external radiotherapy to the jaw and with at least 60 months of follow-up after finishing radiation therapy. Those who died before the 60-month follow-up, or who did not undergo external radiation or received doses lower than 60 Gy, were excluded from the analysis. A 1:2 case-control matching was targeted. For selecting the controls, CIDs C01–C14 + C31 + C32 + C77.0 between January 1st, 2010, and December 31th, 2014, were used.

A cohort of 419 potential controls was initially selected, of which 43 were included in the study. The median follow-up of the control group was 75.68 months (range 60.0–120.3 months). From the initial cohort, 114 patients were excluded because they had not been treated with radiotherapy: four because of low radiotherapy dose (< 60 Gy), 181 because they died before completing the 60-month follow-up, 57 because they were lost to follow-up, four because they had been treated outside the selection period, 11 because they had not received radiation to the jaws, and five because they were transferred to the case group, as they had been identified with ORN.

Data extraction

The following patient data were recorded: demographic data, histological diagnosis, tumor-node-metastasis (TNM) classification, tumor site, risk factors, pre-treatment oral status, basic radiation parameters, dental treatment, surgical data, diagnosis, stage, therapy, and outcomes.

Dental oncology documentation was reviewed for pre- and post-radiotherapy dental status, and all dental procedures were recorded. All patients received pre-radiotherapy dental oncology service clearance, and if indicated, prophylactic dental extraction were performed and fluoride trays were given as per standard head and neck service operating procedure. The patients' dental records were reviewed, and the patients were divided into three categories: a) no extraction, b) pre-radiotherapy dental extractions, and c) post-radiotherapy dental extractions.

The first post-radiation follow-up was at 4 weeks after treatment completion; subsequently, it was every 3 months in the first year, every 4 months in the second year, and at least twice a year thereafter. Detailed clinical examination of the oral cavity was performed as part of routine oncologic follow-up at every visit, and surveillance imaging was reviewed by a dedicated head and neck radiologist with experience in radiation-associated sequelae such as ORN.

The patients with ORN were divided into grades I, II, and III according to the Notani classification of the extent of the ORN lesion.[15] Grade I is defined as ORN confined to the alveolar bone. Grade II ORN is limited to the alveolar bone and/or the mandible above the level of the mandibular alveolar canal. Grade III ORN extends to the mandible below the level of the mandibular alveolar canal and ORN with a skin fistula and/or a pathologic fracture.

Statistical analysis

Data were analyzed using SPSS version 27 (IBM Corporation, Armonk, USA). Initially, a descriptive analysis of independent variables was performed, and differences in cases and controls were assessed through Fisher's exact test or chi-square test (for categorical variables) and Mann-Whitney test (for the continuous variables age, dose, and follow-up time). The association between independent variables and ORN development was assessed by univariate and multivariate logistic regression. The odds ratio (OR) and 95% confidence interval were computed. The multivariate analysis comprised variables that presented $p < 0.10$ in the univariate analysis and was also controlled for age and gender. Kaplan-Meier cumulative hazard curves were constructed and compared using the log-rank test. The level of statistical significance was $p < 0.05$.

Results

Sample characterization

A total of 19 cases with documented ORN diagnosis and 43 controls met the inclusion criteria. The demographic, disease, and treatment characteristics of the cases and controls are summarized in Table 1. The controls and cases were similar in terms of mean total radiation, age, sex, ethnicity, and radiotherapy modality (Table 1). Squamous cell carcinoma was the predominant histology in the cases (n = 17; 89.5%) and

Table 1. Characteristics of patients with osteoradionecrosis and matched controls.

Variable	Cases (n = 19)	Controls (n = 43)	p-value
Gender			
Male	15 (78.9%)	37 (86.0%)	0.47
Female	4 (21.1%)	6 (14.0%)	
Age			
Mean ± SD	55.86 ± 8.82	60.27 ± 8.99	0.08
Ethnicity			
White	17 (89.5%)	39 (90.7%)	1.00
Black	2 (10.5%)	4 (9.3%)	
Tumor site			
Mouth / oropharynx	17 (89.5%)	20 (46.5%)	0.002
Others	2 (10.5%)	23 (53.5%)	
Diagnosis			
Squamous cell carcinoma	17 (89.5%)	40 (93.0%)	0.63
Others	2 (10.5%)	3 (7.0%)	
Tobacco			
Absent	2 (10.5%)	5 (11.6%)	0.04
Continued through RT	12 (63.2%)	13 (30.2%)	
Stopped before RT	5 (26.3%)	25 (58.1%)	
Alcohol			
Absent	4 (21.1%)	9 (20.9%)	0.60
Continued through RT	4 (21.1%)	5 (11.6%)	
Stopped before RT	11 (57.9%)	29 (67.4%)	
Diabetes Mellitus 2			
Absent	19 (100%)	41 (95.3%)	1.00
Present	0 (0%)	2 (4.7%)	
Tumor bone invasion			
Absent	18 (94.7%)	41 (95.3%)	1.00
Present	1 (5.3%)	2 (4.7%)	
Bone resection			
Absent	15 (78.9%)	36 (83.7%)	0.72
Present	4 (21.1%)	7 (16.3%)	
Tooth extraction			
None	5 (27.8%)	19 (48.7%)	0.13
Before RT	1 (5.6%)	5 (12.8%)	
After RT	12 (66.7%)	15 (38.5%)	
AJCC Stage			
I/II	2 (11.8%)	7 (16.3%)	1.00
III/IV	15 (88.2%)	36 (83.7%)	

Conitnue

Continuation			
Treatment			
Surgery + RT / Chemotherapy	15 (78.9%)	24 (55.8%)	
RT	0 (%)	2 (4.7%)	0.18
RT / Chemotherapy	4 (21.1%)	17 (39.5%)	
RT type			
2D	14 (77.8%)	33 (76.7%)	0.60
3D / IMRT	4 (22.2%)	10 (23.3%)	
RT Dose			
Mean + SD	66.66 ± 4.51	65.58 ± 4.52	0.42
Follow-up status			
Disease-free	12 (63.2%)	36 (83.7%)	
Deceased due to tumor	2 (10.5%)	0 (0%)	0.05
Deceased to other causes / new primary	5 (26.3%)	7 (16.3%)	
Follow-up time			
Mean + SD	90.94 ± 48.06	78.47 ± 16.72	0.33

controls (n = 40; 93.0%) (p = 0.63). Clinical stages III–IV were the most prevalent in cases (n = 15; 88.2%) and controls (n = 36; 83.7%) (p = 1.00). Tumor bone invasion was not a common event in the cases (n = 1; 5.3%) or controls (n = 2; 4.7%) (p = 1.00). Bone resection was also uncommon, being performed in four cases (21.1%) and seven controls (16.3%) (p = 0.72). Among the cases, 15 (78.9%) were treated with combined radiation therapy (with/without chemotherapy) and surgical procedures, compared to 24 patients (55.8%) in the control group (p = 0.18). Only two patients in the control group had a diagnosis of diabetes and none among the cases. Seventeen cases (89.5%) and 38 controls (88.3%) were smokers. The mandibular mean dose (D_{mean}) was available in only five cases from the ORN cohort and 10 cases from the control cohort, as the remaining were treated by conventional (2D) radiation therapy. All cases with ORN received total radiation doses of ≥60 Gy, and this minimal dose was used as an inclusion criterion for the controls. The mean dose of radiotherapy was similar between the cases (66.6 Gy) and the controls (65.5 Gy) (p = 0.42).

Among the cases, 12 had no signs of disease after a mean follow-up of 72.9 months. The remaining seven had died: five from new primary tumors and two from primary tumor recurrence. Among the controls, 36 were alive with no signs of disease after a mean follow-up of 78.33 months. The remaining seven had died: three from new primary tumor recurrence and four from other causes. We had no death directly related to the ORN process.

Follow-up and ORN characterization

The overall median follow-up time was 77.03 months (range 17.2–172.3 months); the median time from the completion of radiotherapy to ORN development was 23.83 months (range, 4.4–127.1 months). Ten cases (52.6%) developed ORN before completing 24 months of the end of radiotherapy. The distribution of ORN grades was as follows: grade I, n = 3 (16.7%); grade II, n = 5 (27.8%); and grade III, n = 10 (55.6%). In one case, the ORN was in the maxilla. The majority was treated with segmental mandibulectomy (10 cases; 52.6%). Two cases (both stage I) were treated only with PENTOCLO therapy (pentoxifylline-tocopherol-clodronate combination), and the remaining patients were treated with combinations of debridement and PENTOCLO (Table 2).

Analysis of risk factors for ORN

A binary logistic regression was performed to investigate the possible risk factors for ORN, including variables with a significant difference between cases

and controls in the chi-square test (Table 1: tumor site and tobacco) and factors previously reported in the literature (tooth extraction and radiotherapy dose) (Table 3). Among the cases, 89% had primary tumors in the oral cavity/oropharynx compared to only 46% among the controls. The other sites included: hypopharynx (9 cases), larynx (3 cases), nasopharynx (1 case), parotid (1 case), cutaneous squamous cell carcinoma with head and neck metastasis (2 cases), and unknown primary tumor (9 cases). Univariate analysis showed that the oral cavity/oropharynx site was associated with 9.77-fold increased risk of ORN development compared to the other sites (p = 0.005). We found a higher prevalence of active smokers after the beginning of radiotherapy among cases compared to controls (12 (63.1%) vs. 13 (30.2%) (p = 0.04)). Univariate analysis showed that being an active smoker was associated with 3.95-fold increased risk of ORN development (p = 0.01). Alcohol consumption was common in both groups: 15 cases (79.0%) vs. 34 controls (79.0%).

No significant differences were observed for radiotherapy dose and tooth extraction history. Among the ORN cases, five patients (26.3%) had no history of dental extraction, dental treatment, or dental infection before the beginning of the ORN process. In one case, there was a pre-radiotherapy extraction. In another case, this information was missing. The remaining cases (n = 12; 66.7%) had a pre-ORN extraction event; in five cases, this was preceded by a severe dental infection. Among the controls, 19 (48.7%) had no history of dental extraction pre- or post-radiotherapy. Five controls (12.8%) underwent only pre-radiotherapy extractions. For four patients, information on dental extractions was missing. Post-radiotherapy extractions were performed in 15 patients (38.5%). Despite no significant difference, a tendency towards increased risk was observed, particularly when the extraction was post-

Table 2. Osteoradionecrosis features

Variable	Case (n = 19)
Site	
Mandible	18 (78.9%)
Maxilla	1 (21.1%)
ORN Grade	
I	3 (16.7%)
II	5 (27.8%)
III	10 (55.6%)
Treatment	
Mandibulectomy	10 (52.6%)
PENTOCLO	2 (10.5%)
Debridement + PENTOCLO	7 (36.8%)

Table 3. Univariate and multivariate analysis of risk factors for ORN between cases and matched controls.

Variable	Univariate		Multivariate*	
	OR (95%CI)	p-value	0R (95%CI)	p-value
Tumor site				
Others	1	0.005	1	0.01
Mouth / oropharynx	9.77 (2.0 – 47.5)		21.03 (2.0 – 216.9)	
Tobacco				
Absent / Stopped before RT	1	0.01	1	0.24
Continued through RT	3.95 (1.2 – 12.3)		2.52 (0.5 – 12.1)	
Tooth extraction				
None	1		1	
Before RT	0.76 (0.7 – 8.0)	0.82	0.61 (0.0 – 9.9)	0.73
After RT	3.04 (0.8 – 10.5)	0.08	3.18 (0.5 – 17.6)	0.18
RT Dose	1.05 (0.9 – 1.2)	0.42	1.09 (0.9 – 1.2)	0.27

*Controlled for gender and age.

radiotherapy (OR: 3.04; p = 0.08), a risk that was not observed when the extraction was performed pre-radiotherapy (OR: 0.76, p = 0.82).

The multivariate analysis included all the variables discussed above, and the model was controlled for gender and age. The analysis showed that tumor site was the only significant risk factor (OR: 21.03, p = 0.01).

The Kaplan-Meier cumulative hazard curves also corroborated with the logistic regression analysis and demonstrated that both tumor site (p = 0.003) and smoking status (p = 0.03) represented significant risk factors for ORN; for tooth extraction, it appeared that when the procedure was performed after radiotherapy, a tendency for increased risk was observed in the curves, yet it was not statistical significance (p = 0.13) (Figure).

Discussion

We conducted a case-control study, which is an unusual model for analyzing the risk factors for ORN in head and neck cancer treatment. Most of the published literature on this issue is based on retrospective cohort studies, with short or uncertain periods of follow-up after radiotherapy among patients with and without ORN. Some studies even delimit a data collection period, but do not clearly state the mean/median or minimum follow-up time established in the study.[7,10,11,13,16-21] In most other studies, the minimum follow-up time for this group is 6 months,[12,22-25] ranging from 3[26] to 24 months[27] in others.

Based on the high number of cases of ORN after 3 years of follow-up, we attempted to solve this methodological issue by selecting as controls patients with follow-up periods ≥60 months. In some patients, ORN may develop after even longer time.[28] Although a longer follow-up might be desirable, it may not be entirely possible because of the limitation imposed by the survival rate of patients with head and neck cancer. In our sample, five patients (26.3%) developed the complication after 60 months of follow-up. In their study, Monnier et al suggested two peaks of incidence: an initial peak during the first year following treatment and a second peak after 3 years. They noted that all cases observed in non-operated patients occurred during the second peak, with no evidence of trauma. This result underscores the need for long-term follow-up for this type of complication.[28]

Another inclusion criterion we decided to use was selecting control patients with radiotherapy doses ≥ 60 Gy, focused on the jaw. Although previous case series reported ORN cases after receiving total radiation doses < 60 Gy in 25–45% of cases,[7,8,29] recent publications with patient selection after 2000 have reported that almost 100% of ORN cases received total radiation dose ≥ 60 Gy,[2,16,28] as in our sample. In the study by Owosho et al.,[16] not only had all patients who developed ORN received at least 60 Gy radiation to the primary tumor site, but they

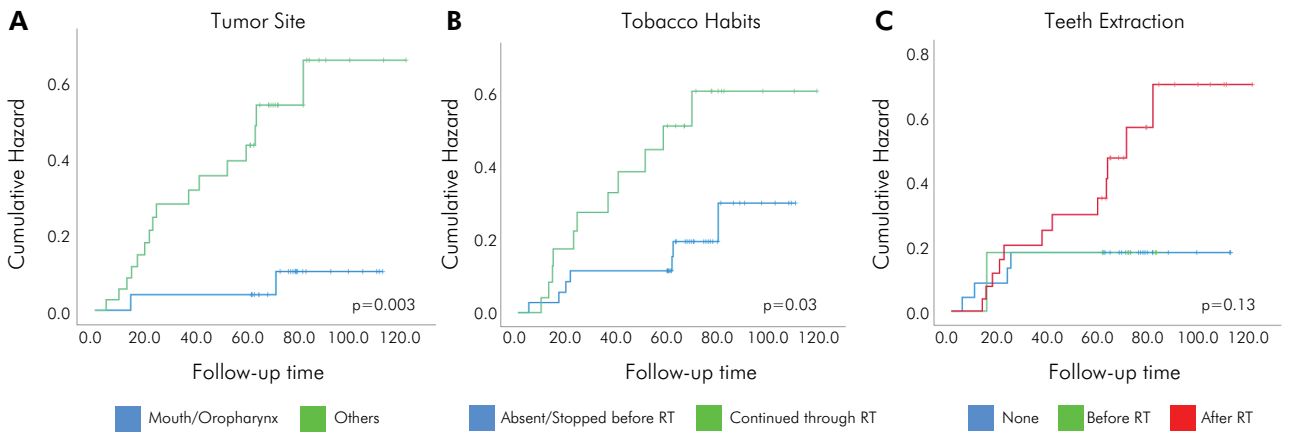

Figure. Kaplan-Meier cumulative hazard curves for tumor site (A), smoking status (B), and tooth extraction (C).

also had similar median times from completion of radiotherapy to diagnosis of ORN (19.1 months (range 0–120.2 months).

Regarding the risk factors for ORN, despite discrepancies among some studies, the majority of them associated higher radiotherapy doses,[13] tobacco[12] and alcohol intake,[25] dental extractions,[12,20,24,25] mandibular osteotomies,[12,18,30,31] and tumor site, [18,20,24-26,31] with a higher risk of ORN. Our results point in the same direction of some cohort studies, with higher risk of ORN among current smokers[11,12,22,27] and among patients treated for oral cavity or oropharyngeal cancers.[18,20,24-26] After multivariate analysis, only tumor site remained statistically significant.

Cigarette smoke contains numerous toxic constituents, such as nicotine and carbon monoxide. Nicotine causes platelet aggregation and vasoconstriction, increasing the risk of microvascular thromboses and decreasing microperfusion. Carbon monoxide competitively inhibits the binding of oxygen to hemoglobin, leading to cellular hypoxia. These toxic substances can undermine the conditions required for wound healing, exacerbating pre-existing tissue damage.[32,33] In our univariate analysis, active smoking was associated with a 3.9-fold increased risk of ORN development. The multidisciplinary team responsible for patient care, which includes head and neck surgeons, radiotherapists, and dentists, among others, should educate patients receiving head and neck radiotherapy about the paramount importance of tobacco cessation before, during, and after treatment. The benefits of tobacco cessation go beyond ORN prevention, yet this tangible outcome can be used as an argument to motivate patients.

The site of the primary tumor influences the amount and location of radiation to the mandible and has been associated with ORN development.[8,29] Based on large case series with more than 100 ORN cases, around 85–90% of ORN cases are found in patients with oral cavity or oropharynx tumors.[8,29] ORN occurs most frequently after radiation therapy of primary tumors of the oral tongue, floor of the mouth, alveolar ridge, retromolar trigone, and tonsils. This aspect is related to the large volume of the mandible included in the primary radiation field in the high-dose ranges for these tumor types, and the surgical approach to resection of tumors in these sites often requires mandibular osteotomies or mandibulectomies that are traumatic to bone tissue [9]. In our multivariate analysis, which was controlled for important factors such as age, gender, radiotherapy dose, tobacco, and teeth extraction history, patients with oral cavity/oropharynx tumors had a 21-fold increased risk of ORN development compared to patients with tumors in other sites ($p = 0.01$). Although higher than previously reported risks, similar patterns of risk according to tumor site have been published.[18,26] In current IMRT treatment planning, special attention is paid to the jaw as an organ at risk, to reduce irradiation without compromising tumor coverage, especially in the treatment of patients with oropharyngeal and oral cavity cancer.

We found no association between dental extractions and risk of ORN ($p = 0.13$). When dental extraction was performed after radiotherapy, a tendency towards increased risk was noted but without statistical significance. Dental extractions, surgery, or other types of trauma frequently precede the onset of ORN. According to the systematic review of Nabil et al.,[1] 7 of 100 patients undergoing post-radiation tooth extraction will develop ORN, and 2 of 100 tooth extractions would lead to ORN. The probable reason is that radiotherapy changes the supporting structures of teeth.[12] However, the rate of spontaneous ORN with no precipitating trauma may be as high as 48–82%[9,16] (25% in our sample). A recent study observed that most spontaneous ORN occurred between 6 months and 2 years after radiotherapy, whereas the risk of developing trauma-induced ORN lasts indefinitely. This observation explains the occurrence of ORN even 10 years after radiotherapy.[3] Although the evidence supports that dental extractions after radiotherapy are a risk factor for ORN, some have also found that extractions before radiotherapy are an independent risk factor for the development of ORN.[10,12,22,34] In this case, the need for pre-radiotherapy extraction is probably a surrogate for the patient's overall poor dental health, predisposing him or her to ORN.

Regarding ORN management, conservative treatment should be limited to early-stage ORN as

proposed by Notani et al.[15] Selected patients should be initially treated by radical surgery, especially those in stage III, with a response of around 10% higher than non-surgical approaches. In our sample, ORN cases were mostly treated by radical surgeries, which was expected, as the majority were advanced-stage cases. Individuals with orocutaneous fistula, pathologic fractures, swelling, or trismus, are expected to have a poor response to conservative treatment.[15,35] At the end of follow-up, disease-free survival was less frequent in the ORN group, mainly because of new primary tumors, without this being statistically significant ($p = 0.05$).

Conclusion

Oral and oropharyngeal primary cancer site was the only risk factor for ORN found in our sample after multivariate analysis. Dental extraction was not an essential event for the development of the pathology, with 28% of ORN patients had not had extractions.

References

1. Nabil S, Samman N. Incidence and prevention of osteoradionecrosis after dental extraction in irradiated patients: a systematic review. Int J Oral Maxillofac Implants. 2011 Mar;40(3):229-43. https://doi.org/10.1016/j.ijom.2010.10.005
2. He Y, Liu Z, Tian Z, Dai T, Qiu W, Zhang Z. Retrospective analysis of osteoradionecrosis of the mandible: proposing a novel clinical classification and staging system. Int J Oral Maxillofac Implants. 2015 Dec;44(12):1547-57. https://doi.org/10.1016/j.ijom.2015.04.006
3. Nabil S, Samman N. Risk factors for osteoradionecrosis after head and neck radiation: a systematic review. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012 Jan;113(1):54-69. https://doi.org/10.1016/j.tripleo.2011.07.042
4. Chronopoulos A, Zarra T, Ehrenfeld M, Otto S. Osteoradionecrosis of the jaws: definition, epidemiology, staging and clinical and radiological findings. A concise review. Int Dent J. 2018 Feb;68(1):22-30. https://doi.org/10.1111/idj.12318
5. Støre G, Boysen M. Mandibular osteoradionecrosis: clinical behaviour and diagnostic aspects. Clin Otolaryngol Allied Sci. 2000 Oct;25(5):378-84. https://doi.org/10.1046/j.1365-2273.2000.00367.x
6. Rogers SN, D'Souza JJ, Lowe D, Kanatas A. Longitudinal evaluation of health-related quality of life after osteoradionecrosis of the mandible. Br J Oral Maxillofac Surg. 2015 Nov;53(9):854-7. https://doi.org/10.1016/j.bjoms.2015.07.008
7. Reuther T, Schuster T, Mende U, Kübler A. Osteoradionecrosis of the jaws as a side effect of radiotherapy of head and neck tumour patients: a report of a thirty year retrospective review. Int J Oral Maxillofac Surg. 2003 Jun;32(3):289-95. https://doi.org/10.1054/ijom.2002.0332
8. Chronopoulos A, Zarra T, Tröltzsch M, Mahaini S, Ehrenfeld M, Otto S. Osteoradionecrosis of the mandible: a ten year single-center retrospective study. J Craniomaxillofac Surg. 2015 Jul;43(6):837-46. https://doi.org/10.1016/j.jcms.2015.03.024
9. O'Dell K, Sinha U. Osteoradionecrosis. Oral Maxillofac Surg Clin North Am. 2011 Aug;23(3):455-64. https://doi.org/10.1016/j.coms.2011.04.011
10. Aarup-Kristensen S, Hansen CR, Forner L, Brink C, Eriksen JG, Johansen J. Osteoradionecrosis of the mandible after radiotherapy for head and neck cancer: risk factors and dose-volume correlations. Acta Oncol. 2019 Oct;58(10):1373-7. https://doi.org/10.1080/0284186X.2019.1643037
11. Tsai CJ, Hofstede TM, Sturgis EM, Garden AS, Lindberg ME, Wei Q, et al. Osteoradionecrosis and radiation dose to the mandible in patients with oropharyngeal cancer. Int J Radiat Oncol Biol Phys. 2013 Feb;85(2):415-20. https://doi.org/10.1016/j.ijrobp.2012.05.032
12. Sathasivam HP, Davies GR, Boyd NM. Predictive factors for osteoradionecrosis of the jaws: A retrospective study. Head Neck. 2018 Jan;40(1):46-54. https://doi.org/10.1002/hed.24907
13. Pereira IF, Firmino RT, Meira HC, Vasconcelos BC, Noronha VR, Santos VR. Osteoradionecrosis prevalence and associated factors: a ten years retrospective study. Med Oral Patol Oral Cir Bucal. 2018 Nov;23(6):e633-8. https://doi.org/10.4317/medoral.22310
14. Zevallos JP, Mallen MJ, Lam CY, Karam-Hage M, Blalock J, Wetter DW, et al. Complications of radiotherapy in laryngopharyngeal cancer: effects of a prospective smoking cessation program. Cancer. 2009 Oct;115(19):4636-44. https://doi.org/10.1002/cncr.24499
15. Notani K, Yamazaki Y, Kitada H, Sakakibara N, Fukuda H, Omori K, et al. Management of mandibular osteoradionecrosis corresponding to the severity of osteoradionecrosis and the method of radiotherapy. Head Neck. 2003 Mar;25(3):181-6. https://doi.org/10.1002/hed.10171
16. Owosho AA, Tsai CJ, Lee RS, Freymiller H, Kadempour A, Varthis S, et al. The prevalence and risk factors associated with osteoradionecrosis of the jaw in oral and oropharyngeal cancer patients treated with intensity-modulated

radiation therapy (IMRT): The Memorial Sloan Kettering Cancer Center experience. Oral Oncol. 2017 Jan;64:44-51. https://doi.org/10.1016/j.oraloncology.2016.11.015
17. Chen JA, Wang CC, Wong YK, Wang CP, Jiang RS, Lin JC, et al. Osteoradionecrosis of mandible bone in patients with oral cancer—associated factors and treatment outcomes. Head Neck. 2016 May;38(5):762-8. https://doi.org/10.1002/hed.23949
18. Kuhnt T, Stang A, Wienke A, Vordermark D, Schweyen R, Hey J. Potential risk factors for jaw osteoradionecrosis after radiotherapy for head and neck cancer. Radiat Oncol. 2016 Jul;11(1):101. https://doi.org/10.1186/s13014-016-0679-6
19. Renda L, Tsai TY, Huang JJ, Ito R, Hsieh WC, Kao HK, et al. A nomogram to predict osteoradionecrosis in oral cancer after marginal mandibulectomy and radiotherapy. Laryngoscope. 2020 Jan;130(1):101-7. https://doi.org/10.1002/lary.27870
20. Kojima Y, Yanamoto S, Umeda M, Kawashita Y, Saito I, Hasegawa T, et al. Relationship between dental status and development of osteoradionecrosis of the jaw: a multicenter retrospective study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2017 Aug;124(2):139-45. https://doi.org/10.1016/j.oooo.2017.04.012
21. Studer G, Bredell M, Studer S, Huber G, Glanzmann C. Risk profile for osteoradionecrosis of the mandible in the IMRT era. Strahlenther Onkol. 2016 Jan;192(1):32-9. https://doi.org/10.1007/s00066-015-0875-6
22. Moon DH, Moon SH, Wang K, Weissler MC, Hackman TG, Zanation AM, et al. Incidence of, and risk factors for, mandibular osteoradionecrosis in patients with oral cavity and oropharynx cancers. Oral Oncol. 2017 Sep;72:98-103. https://doi.org/10.1016/j.oraloncology.2017.07.014
23. Lee IJ, Koom WS, Lee CG, Kim YB, Yoo SW, Keum KC, et al. Risk factors and dose-effect relationship for mandibular osteoradionecrosis in oral and oropharyngeal cancer patients. Int J Radiat Oncol Biol Phys. 2009 Nov;75(4):1084-91. https://doi.org/10.1016/j.ijrobp.2008.12.052
24. Wang TH, Liu CJ, Chao TF, Chen TJ, Hu YW. Risk factors for and the role of dental extractions in osteoradionecrosis of the jaws: A national-based cohort study. Head Neck. 2017 Jul;39(7):1313-21. https://doi.org/10.1002/hed.24761
25. Willaert R, Nevens D, Laenen A, Batstone M, Politis C, Nuyts S. Does intensity-modulated radiation therapy lower the risk of osteoradionecrosis of the jaw? A long-term comparative analysis. Int J Oral Maxillofac Implants. 2019 Nov;48(11):1387-93. https://doi.org/10.1016/j.ijom.2019.04.018
26. Kubota H, Miyawaki D, Mukumoto N, Ishihara T, Matsumura M, Hasegawa T, et al. Risk factors for osteoradionecrosis of the jaw in patients with head and neck squamous cell carcinoma. Radiat Oncol. 2021 Jan;16(1):1. https://doi.org/10.1186/s13014-020-01701-5
27. Caparrotti F, Huang SH, Lu L, Bratman SV, Ringash J, Bayley A, et al. Osteoradionecrosis of the mandible in patients with oropharyngeal carcinoma treated with intensity-modulated radiotherapy. Cancer. 2017 Oct;123(19):3691-700. https://doi.org/10.1002/cncr.30803
28. Monnier Y, Broome M, Betz M, Bouferrache K, Ozsahin M, Jaques B. Mandibular osteoradionecrosis in squamous cell carcinoma of the oral cavity and oropharynx: incidence and risk factors. Otolaryngol Head Neck Surg. 2011 May;144(5):726-32. https://doi.org/10.1177/0194599810396290
29. Curi MM, Dib LL. Osteoradionecrosis of the jaws: a retrospective study of the background factors and treatment in 104 cases. J Oral Maxillofac Surg. 1997 Jun;55(6):540-4. https://doi.org/10.1016/S0278-2391(97)90478-X
30. Raguse JD, Hossamo J, Tinhofer I, Hoffmeister B, Budach V, Jamil B, et al. Patient and treatment-related risk factors for osteoradionecrosis of the jaw in patients with head and neck cancer. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016 Mar;121(3):215-21.e1. https://doi.org/10.1016/j.oooo.2015.10.006
31. Liao PH, Chu CH, Tang PL, Wu PC, Kuo TJ. Preradiation tooth extraction and jaw osteoradionecrosis: nationwide population-based retrospective study in Taiwan. Clin Otolaryngol. 2020 Nov;45(6):896-903. https://doi.org/10.1111/coa.13624
32. Shuler RL. Effect of cigarette smoking on the circulation of the oral mucosa. J Dent Res. 1968 Nov-Dec;47(6):910-5. https://doi.org/10.1177/00220345680470065201
33. Silverstein P. Smoking and wound healing. Am J Med. 1992 Jul;93(1 1A):22S-4S. https://doi.org/10.1016/0002-9343(92)90623-J
34. Chang DT, Sandow PR, Morris CG, Hollander R, Scarborough L, Amdur RJ, et al. Do pre-irradiation dental extractions reduce the risk of osteoradionecrosis of the mandible? Head Neck. 2007 Jun;29(6):528-36. https://doi.org/10.1002/hed.20538
35. Oh HK, Chambers MS, Martin JW, Lim HJ, Park HJ. Osteoradionecrosis of the mandible: treatment outcomes and factors influencing the progress of osteoradionecrosis. J Oral Maxillofac Surg. 2009 Jul;67(7):1378-86. https://doi.org/10.1016/j.joms.2009.02.008