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Original Research

Osteoradionecrosis of mandible bone in patients with oral cancer-associated factors and treatment outcome: An original research

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ABSTRACT:
Aim: The purpose of the present research was to assess the various risk factors and treatment outcomes in the patients affected by osteoradionecrosis. **Methodology:** This retrospective hospital-based study was performrd in CCM hospital, Nehru Nagar, Bhilai. The case-control study involves 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. **Results:** 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). **Conclusion:** 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.

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INTRODUCTION

Radiation therapy (RT) plays a key role in the management of head and neck cancers resulting in improved tumor control and increased survival rates.[1] Despite these advances, patients treated with RT often develop radiation-associated toxicities such as osteoradionecrosis (ORN).[2,3] In this condition, bone within the radiation field becomes devitalized and exposed through the overlying skin or mucosa that persist as a non-healing area. The history of ORN dates back 100 years when it was first noted by Regaud in 1922.[4] Although rare, ORN is one of the most dreaded complications of head and neck RT that can significantly impact quality of life. [5,6] Based on its clinical presentation and observation, ORN can be defined as occurring when 'irradiated bone becomes devitalised and exposed through the overlying skin or mucosa without healing for 3 months, without recurrence of a tumour'.[7] Despite this definition being the most frequently used, clinicians argue that it is not complete as it disregards radiological or histological findings consistent with ORN.[8] Using radiological and histological means to diagnose ORN is also disputed, adding more controversy to the definition.[9] A minority of patients who develop ORN are seen with radiologically altered bone yet clinically intact mucosa.[7] It is therefore difficult to define the outlying cases of ORN. Others define ORN as consisting of an area of more than 1cm which has healed for more than six months. This definition has led to the implementation of the 'watch and wait' protocol to fulfil diagnostic criteria. One could argue that it would be illogical to approach this protocol if early intervention and control of the disease can be delivered.[10] Nevertheless, an overall consensus has been reached among authors with regards to the presence of devitalised and necrotic bone in their definitions of ORN.[9] Newer theories of the

pathogenesis of ORN have been established, adding to the portfolio of theories that have been proposed for the last 80 years. These theories still influence the ongoing development of medical treatment options.[11] Marx proposed that tissues, following RT, undergo the process of hypocellularisation. RT leads to cellular death of both soft and hard tissues from direct radiation damage, as well as hypovasularisation of arterioles and arteries due to endarteritis obliterans. Gradual tissue ischaemia and hypoxia consequently give rise to a reduction of the reparative and synthetic capacity of irradiated tissues, eventually producing a non-healing wound.[10] In summary, irradiated tissues are left insufficiently perfused, fibrotic, fragile, and hypocellular. This increases the risk of developing ORN if trauma-induced inflammation occurs.[8] Risk factors that predispose patients to ORN are multifactorial and can differ with regards to severity. Despite a lack of clinical studies, risk factors have been implicated and identified in the literature. These risk factors can either be systemic or local. The former is associated with the development of oral cancers and can include malnutrition, immunodeficiency, chronic alcohol abuse, and a long-term smoking history. The latter refers to events that occur intra-orally, such as the site and size of the tumour, RT site and dosage, poor oral hygiene and dentition, radiation-induced xerostomia, and periodontal disease.[10] A strong risk factor for the development of ORN is dental alveolar surgery post-RT, namely, dental extractions and implantations. Around 5% of ORN cases are trauma-induced from dental extractions. For the treatment of tumours near to or involving the mandible, mandibular surgery is another predisposing risk factor for ORN as tissues may struggle to heal post-RT. A well-recognised risk factor for the occurrence of ORN is dose of RT. Studies have shown that the higher the dose of RT, the higher the risk of ORN. RT doses to the mandible ranging between 60 and 70 Gy have been heavily associated with the incidence of ORN, while ORN sites that received doses of 50–60 Gy are fewer in number. With hyper-fractionated RT doses > 70 Gy, reports have shown that incidences of ORN are lower than those of the abovementioned doses.[10]The fibro-atrophic theory has served to provide avenues for newer medical management approaches to ORN.[11] Tocopherol (vitamin E) serves to minimise the production and regeneration of ROS by protecting cell membranes from oxidative stress due to lipid breakdown. Tocopherol works remarkably well with pentoxifylline, in promoting collagen synthesis and reducing fibrosis. It works by vasodilating vessel reperfusion tissues and inhibits TNFα production. Surgery for ORN is usually reserved for Notani stage III cases which may present with pathological fractures of the mandible or an orocutaneous fistula. For these patients, restoring an adequate blood supply with resection of non-vital bone and a free bony tissue transfer may be the only plausible treatment option. With regards to management of advanced ORN of the mandible, the most preferred treatment is an osteocutaneous fibula free flap reconstruction. [12]

AIM OF THE PRESENT STUDY

The purpose of the present research was to assess the various risk factors and treatment outcomes in the patients affected by osteoradionecrosis.

METHODOLOGY

This retrospective hospital-based study was performrd in CCM hospital, Nehru Nagar, Bhilai. 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 2015 and December 2022. 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. 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). 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. 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). Kaplan- Meier cumulative hazard curves were constructed and compared using the log-rank test. The level of statistical significance was $p < 0.05$.

RESULTS

A total of 19 cases with documented ORN diagnosis and 43 controls met the inclusion criteria. The controls and cases were similar in terms of mean total radiation, age, sex, ethnicity, and radiotherapy modality. Squamous cell carcinoma was the predominant histology in the cases (n = 17; 89.5%) and 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). 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). 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, 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). Among the cases, 12 had no signs of disease after a mean follow-up of 72.9 months. 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). The majority was treated with segmental mandibulectomy (10 cases; 52.6%). Two cases (both stage I) were treated only with PENTOCLO therapy (pentoxifylline-tocopherolclodronate combination), and the remaining patients were treated with combinations of debridement and PENTOCLO. (Table 1)

Table 1- 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%)

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)). Alcohol consumption was common in both groups: 15 cases (79.0%) vs. 34 controls (79.0%). Among the controls, 19 (48.7%) had no history of dental extraction pre- or post-radiotherapy. The analysis showed that tumor site was the only significant risk factor (OR: 21.03, p = 0.01). (Table 2)

Table 2- Univariate and multivariate analysis of risk factors for ORN between cases and matched controls

Variable	Univariate		Multivariate	
	OR (95%CI)	p-value	OR (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

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. Furthermore, a retrospective study done by Lee et al. analysed the 'dose-effect' association for ORN of the mandible and recognised an increase in the incidence of ORN in patients who received a tumour radiation dose of >54 Gy.[13] Tsai et al. suggested in their study that a reduced risk of ORN may be apparent if a dose of <50 Gy was delivered to the whole mandible.[14] This suggestion could be further studied in the future. Newer methods of delivering RT,

such as IMRT techniques, have given rise to fewer ORN cases compared to traditional two-beam techniques.[15] It is believed that this difference is due to the ability to contour radiation waves around and away from the mandible and salivary
glands. This encourages the lowest total doses to these areas. Sparing of the salivary glands is a measure for the prevention of xerostomia and subsequent ORN.[16,17] Regarding the risk factors for ORN, despite discrepancies among some studies, the majority of them associated higher radiotherapy doses, tobacco and alcohol intake, dental extractions, mandibular osteotomies, and tumor site, 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 and among patients treated for oral cavity or oropharyngeal cancers. After multivariate analysis, only tumor site remained statistically significant. The site of the primary tumor influences the amount and location of radiation to the mandible and has been associated with ORN development. 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. Regarding ORN management, conservative treatment should be limited to early-stage ORN as proposed by Notani et al. 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.[18] In our sample, ORN cases were mostly treated by radical surgeries, which was expected, as the majority were advanced-stage cases.

CONCLUSION

Oral and oropharyngeal primary cancer site was the only risk factor for ORN found in our sample after multivariate analysis. 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.

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