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Parameters Associated With Mandibular Osteoradionecrosis

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Abstract: The objective of this review is to discuss factors related to the risk of osteoradionecrosis (ORN) and how to minimize the likelihood of this complication. A PubMed search for publications pertaining to ORN within the last 3 years was conducted revealing 44 publications. The bibliographies of these publications were reviewed to identify additional references spanning a longer time period. The incidence of ORN is 5% to 10% with a median latency period of 1 to 2 years or less. The likelihood of ORN depends on a number of factors including primary site and extent of disease, dental status, treatment modality, radiotherapy (RT) dose, volume of mandible included in the planning target volume, RT fractionation schedule and technique, and teeth extractions. The risk of ORN may be reduced by limiting the RT dose and volume of mandible irradiated without increasing the risk of a local-regional recurrence due to a marginal miss.

Key Words: mandibular osteoradionecrosis, radiotherapy, mandible, teeth extraction, head and neck cancer

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Osteoradionecrosis (ORN) is a significant late complication of radiotherapy (RT) and may occur in any irradiated bone months to years after treatment.[1–4] ORN has been defined in various ways. Generally, ORN is RT-induced bone exposure in the absence of a local recurrence. Because high-dose RT alone or in conjunction with surgery and/or chemotherapy is an integral component of the treatment of head and neck cancer, ORN is a late complication sometimes experienced by these patients and, when it occurs, it usually involves the mandible.[5–11]

The management of patients with ORN is complex and depends on the severity of the complication and the likelihood that the intervention will be successful. Patients with an asymptomatic bone exposure may be managed with observation or pentoxifylline alone or combined with antibiotics.[12] Those with more advanced ORN may benefit from debridement, sequestrectomy, more extensive surgical procedures including segmental mandibulectomy and bony free-flap reconstruction, hyperbaric oxygen therapy alone, before and/or after surgery or a combination of these procedures. The probability of successful intervention is variable and many of these patients will struggle with persistent ORN for the remainder of their lives. Therefore, an attractive strategy is avoidance.

The aim of this paper is to discuss factors that are associated with the development of ORN and how to minimize the risk of this complication without increasing the odds of a local-regional recurrence.

MECHANISM

ORN occurs in irradiated bone when it is compromised due to hypovascularity, hypoxia, and hypocellularity, which occurs as a result of fibrosis, endarteritis, and periarteritis.[2] Tissue breakdown occurs when collagen lysis and cell death are greater than cellular replication,[2] in a process characterized by destruction of osteocytes, absence of osteoblasts, and lack of newly formed osteoid tissue. ORN may be due to trauma, such as a dental extraction or sharp ridges associated with a suboptimal alveoplasty, or it may occur spontaneously.[2,13] Although ORN is thought by some to be due to osteomyelitis, microorganisms are likely to play a minor role and are probably surface contaminants.[2] Marx[2] observed that ORN is more like a chronic diabetic ulcer than osteomyelitis. Because of the complexity of the pathogenic process, it is impossible to define a clear separation between pathologic and healthy marrow. Osteocytes and blood vessels are often irreversibly compromised, but damaged bone can sometimes recover.

GRADING

The severity of ORN may be graded as follows: (1) cortical plate exposure, heals within 3 months; (2) cortical plate

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exposure, heals after >3 months; (3) cortical bone involvement, radiographic abnormality, or conservative treatment (debridement, hyperbaric oxygen); (4) full thickness bone involvement or heals with aggressive surgery such as segmental mandibulectomy and free-flap reconstruction; (5) ORN persists despite aggressive surgery; and (6) death from ORN.[5] However, many staging systems for ORN exist.[14]

Although the Common Terminology Criteria for Adverse Events version 4 may be used, it is not as clinically useful as those mentioned above.

INCIDENCE AND LATENCY

Reuther et al[15] reported on 830 patients who received RT at the University of Heidelberg between 1969 and 1999; 68 patients (8.2%) developed ORN. The median interval between treatment and ORN was 13 months (range, 2 to 122 mo). Lee et al[16] reported on 198 patients treated with surgery and RT (101 patients, 51%) or definitive RT (97 patients, 49%) at Yonsei University (Seoul); 13 patients (6.6%) developed ORN with a median latency of 22 months (range, 1 to 69 mo). Tsai et al[17] reported on 402 patients with T1 and T2 oropharyngeal cancers treated with definitive RT between 2000 and 2008 at the MD Anderson Cancer Center (Houston); 30 patients (7.5%) developed ORN after a median interval of 8 months (range, 0 to 71 mo). Thus, the median latency period is 1 to 2 years or less with a wide range.

PARAMETERS RELATED TO ORN

The proportion of patients who develop mandibular ORN is likely 5% to 10% and will vary with RT dose and with the amount of mandible that is included in the planning target volume, which will in turn depend on the primary site and extent of disease.[4,18–20] Patients with cancers of the oral cavity and oropharynx are likely at highest risk; those with cancers of the larynx, hypopharynx, and paranasal sinuses are probably less so depending on disease extent.[18,19] Newer RT techniques, such as intensity-modulated radiotherapy (IMRT) and proton beam irradiation, allow for more conformal treatment volumes that may include less mandible receiving high irradiation doses thus potentially decreasing the likelihood of ORN.

Other parameters that may influence the likelihood of ORN include dental status, teeth extractions, mandibular surgery, RT dose to the mandible, and length of follow-up. Additional factors may include sex, tobacco and/or alcohol use, and treatment modality (definitive RT, surgery and postoperative RT, preoperative RT and surgery).[15] Gomez et al[20] reported on 168 patients treated with IMRT between 2000 and 2007 at the Memorial Sloan Kettering Cancer Center (New York) for cancers of the oral cavity (36 patients), nasopharynx (25 patients), larynx/hypopharynx (31 patients), paranasal sinuses (35 patients), and oropharynx (41 patients). All had a pretreatment dental evaluation and those who were dentulous were placed on a fluoride regimen. Seventy-one patients (42%) also had surgery and 110 patients (65%) had adjuvant chemotherapy. Pretreatment extractions were performed in 30 patients (18%) and 7 patients (4%) were edentulous. Median maximum mandibular dose was 67.98 Gy and median mean mandibular dose was 38.45 Gy. Median follow-up was 37.4 months (range, 0.8 to 89.6 mo). Two patients, both with oral cavity primaries, developed ORN. Neither had pretreatment extractions. Thus, the overall risk was 2 (1.2%) of 168 patients overall and 2 (5.5%) of 36 patients with oral cavity cancers. The maximum mandibular doses for these 2 patients were 71.83 and 68.28 Gy, respectively, while the mean mandibular doses were 58.12 and 53.35 Gy, respectively.

Wang et al[21] reported on 23,527 patients included in the Taiwan National Health Insurance Research Database who were treated with RT for head and neck cancer between 1995 and 2011. ORN was observed in 1719 patients (7.3%) with an incidence of 3.93 per 100 person-years. The risk was highest for patients treated for buccal mucosa cancer. Whereas the risk of ORN was not impacted by pre-RT tooth extractions, it was associated with post-RT extractions with a gradually increasing risk that peaked at 4 to 5 years. The use of steroids was associated with a reduced risk of ORN. The length of steroid use was not specified.

Kuo et al[22] reported on a retrospective cohort of 1759 patients with head and neck cancer treated with RT from a random sample of 1,000,000 insurants in the Taiwan National Health Insurance Database from 2000 to 2013. Post-RT dental extractions were performed in 522 patients and 1237 patients were without post-RT extractions. Moderate to severe ORN developed in 39 (2.2%) of 1759 patients during an average of 3.02 years (range, 0.62 to 8.89 y). ORN was observed in 27 (5.1%) of 522 patients with post-RT extractions and 12 (0.97%) of 1237 without post-RT extractions. ORN was observed in 9 (2.4%) of 373 patients with post-RT extractions who had 5 or fewer teeth removed compared with 18 (12.1%) of 149 patients who had 6 or more teeth extracted ($P < 0.0001$). Patients who had post-RT extractions within 6 months had a significantly higher risk of ORN compared with those for whom the interval exceeded 6 months ($P < 0.0315$).

Kuhnt et al[18] reported on 776 patients treated with definitive or postoperative RT at the University Hospital Halle-Wittenberg between 2003 and 2013. Primary sites included the nasopharynx, 43 patients; oropharynx, 226 patients; oral cavity, 259 patients; parotid, 34 patients; and hypopharynx/larynx, 214 patients. Postoperative RT doses ranged from 64 to 70 Gy and definitive RT dose were in the range of 77.6 Gy with altered fractionation. Concomitant chemotherapy was used in 365 patients (47%). Moderate to severe ORN developed in 51 patients (6.6%) with a mean latency of 9 months (range, 0 to 90 mo). Bone surgery was required for 90 patients (11.6%). Bone surgery (HR, 5.87) and oral cavity primary site (HR, 4.69) were associated with an increased risk of ORN. The risk of ORN was not significantly related to sex, dentition, or chemotherapy.

Lee et al[16] reported on 198 patients treated with definitive RT or surgery and RT between 1990 and 2000; the median RT dose was 60 Gy. The likelihood of ORN was significantly increased for those who had mandibular surgery ($P = 0.001$) and for those who a biologically equivalent dose of >54 Gy at 1.8 Gy per fraction ($P = 0.008$). De Felice et al[23] reported on 36 patients who developed ORN and were treated at St Thomas' Hospital (London) between 2009 and 2014. The ORN volumes were contoured on the treatment planning CTs for the near maximum dose (D2%), minimum dose (D_{min}), mean dose (D_{mean}), and percentage of bone receiving 50 Gy (V50). The authors evaluated the impact of these parameters on ORN persistence and resolution. The median interval from the end of RT to ORN was 6 months. The percentage of patients with mandibular ORN was 61%. The D_{mean} to the effected bone was 57.6 Gy and 44% had a D2% of 65 Gy or greater. Smoking was associated with ORN persistence on univariate analysis. No factors were found to impact ORN resolution or progression on logistic regression.

Tsai et al[17] performed a nested case control comparison of ORN versus ORN free patients matched for age, sex, RT

type, treatment year, and cancer subsite from a series of 402 patients treated with definitive RT for T1 and T2 oropharyngeal cancers. The analysis included the volume of mandible that received 10 to 60 Gy in 10 Gy increments. Adequate detailed RT plans were available for 25 of 30 ORN patients who were then matched to 40 controls. ORN patients had significantly higher mandibular volumes that received 60 Gy and especially 50 Gy ($P = 0.02$) compared with ORN free patients after adjusting for dental factors such as whether patients were dentate pre-RT and whether pre-RT extractions were performed.

Chang et al[5] reported on 413 patients treated with definitive RT between 1987 and 2002 for carcinomas of the oropharynx and from an unknown mucosal primary site at the University of Florida (Gainesville, FL). Patients were excluded if they had a local recurrence after RT, additional RT above the clavicles, head, and neck surgery other than a neck dissection, or were treated with IMRT which was used for some patients with head and neck cancers after September 2001. Patients underwent a thorough dental evaluation before treatment; teeth in marginal condition in parts of the mandible and maxilla likely to receive high RT doses were extracted. The dose to the mandibular arch planned to receive high-dose RT was calculated. The median RT dose was 75.6 Gy (range, 50 to 81.6 Gy); altered fractionation was used in 327 patients (79%). Twenty patients (4.8%) received a brachytherapy boost. Sixty-six patients (16%) received adjuvant chemotherapy. Pre-RT extractions were performed in 163 patients (39%). The endpoint of the study was ORN grade 2 or higher with grade 2 being defined as exposed cortical plate requiring > 3 months to heal. Variables included in the multivariate analysis included brachytherapy boost, adjuvant chemotherapy, RT dose (< 70 vs. 70 Gy or more), fractionation (once-daily vs. altered), ipsilateral versus bilateral field arrangement, proportion of mandibular arch in high-dose boost volume (≤ 0.6 vs. > 0.6), pre-RT extractions, T-stage, weight loss, and dental risk group. Median follow-up was 3.8 years (range, 0.3 to 17.4 y); minimum follow-up for survivors was 2 years. The incidence of ORN was: edentulous, 0.8%; teeth in-field with pre-RT extractions, 15%; and teeth in-field without pre-RT extractions, 9%; and overall, 9%. Overall, 51 (19%) of 271 patients who retained their mandibular teeth following RT required post-RT extractions. Ten (24%) of 41 patients with in-field teeth who required post-RT extractions developed ORN compared with 22 (11%) of 198 patients who did not require post-RT extractions ($P = 0.087$). Multivariate analysis revealed that the following factors were significantly related to an increased risk of ORN: RT dose of 70 Gy or more ($P = 0.0054$); once-daily fractionation ($P = 0.0004$); brachytherapy boost ($P = 0.0002$); and pre-RT extractions ($P = 0.00154$).

Schuurhuis et al[24] reported on a retrospective study including 185 consecutive patients treated with definitive or postoperative RT at the University of Groningen from 2004 to 2008. The prescribed mean dose to the target was 64 Gy (range, 50 to 70 Gy). Patients with periodontal pockets 6 mm or more had an increased risk of ORN (19%), especially when the pretreatment strategy consisted of initial periodontal therapy (33%) rather than removal of these teeth (14%) emphasizing the importance of aggressive preventive strategies.

Goldwaser et al[25] reported on 82 treated at the Massachusetts General Hospital (Boston) between 1984 and 2005. Multivariate analysis revealed that increased body mass index ($P = 0.02$) and the use of steroids ($P = 0.02$) were associated with a reduced risk of ORN and RT dose of > 66 Gy was associated with an increased risk of ORN ($P = 0.03$).

Gevorgyan et al[26] reported on 1575 patients who had received RT for head and neck cancer and were evaluated in the Departments of Otolaryngology and Dentistry at Sunnybrook Health Sciences Centre (Toronto) between 2003 and 2009. Mandibular ORN was observed in 14 patients (0.89%) and was not significantly related to sex ($P = 0.139$), smoking ($P = 0.514$), alcohol use ($P = 0.583$), tumor site ($P = 0.381$), T-stage ($P = 0.429$), N-stage ($P = 0.643$), overall American Joint Committee on Cancer stage ($P = 0.231$), or treatment modality ($P = 0.231$). Treatment modality was stratified as surgery and RT, RT, and chemoradiation. IMRT was associated with less severe ORN compared with conventional RT.

Monroe et al[19] reported on 89 patients treated with IMRT at the Penrose Cancer Center (Colorado Springs) between 2008 and 2014. RT dose was prospectively calculated for tooth bearing parts of the mandible and maxilla. The median dose was 70 Gy (range, 58 to 70 Gy); median follow-up was 2.5 years (range, 0.2 to 6.9 y). ORN was observed in 4 (4.5%) patients. Univariate analysis revealed that the likelihood of ORN was not related to alcohol intake, heart disease, diabetes, hypertension, lung disease, sex, baseline dental condition, prior oral surgery for cancer, tobacco use, chemotherapy, T-stage, or age. Only oral cavity primary site ($P = 0.0314$) and RT dose ($P = 0.0165$) were associated with an increased risk of ORN.

Ben-David et al[27] analyzed dosimetric and clinical predictors of mandibular ORN in a series of 176 patients treated with parotid sparing IMRT at the University of Michigan (Ann Arbor) who underwent a meticulous prophylactic dental assessment and care according to a uniform policy. These measures included extractions of high risk, periodontally diseased, and unrestorable teeth in parts of the mandible expected to receive high-RT doses, fluoride supplements, and the placement of guards aimed to reduce electron backscatter off of metal dental restorations. IMRT was used to produce a dose gradient across the mandible in all patients so that the bone dosimetry was improved compared that obtained with 2 or 3 dimensional techniques. The dose to 1% of the mandible was 65 and 70 Gy in 75% and 50% of patients, of whom 7% had undergone teeth extractions after RT. No case of ORN was diagnosed at a median follow-up of 34 months.

On the basis of 22 randomized controlled trials, a total of 117 cases of ORN from among 5742 irradiated head and neck cancer patients were recorded by Nabil and Samman,[28] giving an incidence rate of 2%. In this study, the addition of chemotherapy agents to RT did not appear to increase the risk of developing ORN. In contrast, when subjects who received curative RT were compared with those receiving adjuvant RT, no important difference in the risk of developing ORN was seen. This systematic review concluded that there was no difference in the risk of developing ORN with the use of accelerated fractionation without dose reduction, but when accelerated fractionation with total dose reduction was used, there was a reduction in ORN incidence compared with conventional fractionation, a finding that is expected owing to the total dose reduction.

DISCUSSION

As outlined above, a number of variables are likely related to the risk of ORN (Table 1). The clinician may be able to modify some, depending on the location and extent of the tumor, including mandibular dose and volume, fractionation schedule, combining surgery and RT versus RT alone, and post-RT extractions. Some variables cannot be modified including the patient's dental condition at diagnosis and relationship of the tumor to the mandible and remaining dentition. Although pre-RT extractions may not reduce the risk of ORN,

TABLE 1. Literature Review of Studies Evaluating ORN

References and Institution	No. Patients	Primary Sites	Follow-up	ORN Incidence (%)	Significant Factors
Gomez et al,[20] MSKCC	168	OC, NPX, LX, HPX, PS, OPX	Median 37.4 mo	1.2	Maximum and mean mandibular dose
Gevorgyan et al,[26] Sunnybrook	1575	Various	NS	0.89	Risk decreased after IMRT
Kuo et al,[22] Kaohsiung Veterans General Hospital	1759	Various	Mean 3.02 y	2.2	Post-RT extractions, no. teeth extracted, extractions within 6 mo
Tsai et al,[17] MD Anderson Hospital	402	T1-T2 OPX	NS	7.4	Mandibular volume receiving 50 Gy
Monroe et al,[19] Penrose Cancer Hospital	89	Various	Median 2.5 y	4.5	OC primary site, RT dose
Chang et al,[5] University of Florida	413	OPX, unknown primaries	Median 3.8 y	9	RT dose of >70 Gy, QD fractionation, brachytherapy boost, pre-RT extractions
Kuhnt et al,[18] Hospital Halle-Wittenberg	776	NPX, OPX, OC, parotid, HPX/LX	NS	6.6	Bone surgery, OC primary site
Ben-David et al,[27] University of Michigan	176	Various	Median, 34 mo	0	NS

HPX indicates hypopharynx; IMRT, intensity-modulated radiotherapy; LX, larynx; MSKCC, Memorial Sloan Kettering Cancer Center; NPX, nasopharynx, NS, nonsignificant; OC, oral cavity; OPX, oropharynx; ORN, osteoradionecrosis; PS, paranasal sinus; QD, once-daily fractionation; RT, radiotherapy.

they should be considered when teeth that are likely to be within the high dose volume exhibit 1 or more of the following: extensive caries, moderate to advanced periodontal disease, lack of opposing teeth and consequent loss of function, incomplete eruption and partial impaction, and extensive periapical lesions.[29] Chin et al[30] analyzed the impact of dental restorations on backscatter and found that dental amalgams had little impact while gold had up to 33% dose enhancement that could be absorbed by 3 to 5 mm of tissue equivalent material. It is likely that the tissues most impacted would be the oral tongue and buccal mucosa rather than the mandible, which would be difficult to shield in any event. However, it is important to limit the RT dose to the mandible as much as safely possible, particularly the volume receiving ≥ 70 Gy. Although Wang and colleagues reported a reduced risk of ORN in patients who received steroids, due to the adverse effects of long-term steroid use, they should be avoided in the absence of a clear indication. It is essential to not use planning target volumes that are overly conformal because a patient with a local-regional recurrence due to a marginal miss is not likely to be salvaged. Post-RT extractions of teeth from a part of the mandible that has received high-dose RT should be avoided.

The importance of this preventive strategy becomes clear if one takes into account that the irradiated mandible is susceptible to ORN progression even if the clinical and final histopathologic assessments confirm complete resection of necrotic bone margins. Thus, Zaghi et al[31] observed that despite extensive mandible resection and free-tissue transfer, 8 of 26 (30.8%) patients who histologically were clear of necrotic margins developed persistent ORN.

CONCLUSION

The incidence of ORN is 5% to 10% with a latency period of 1 to 2 years or less. The likelihood of ORN may be decreasing with more modern treatment such as IMRT and proton beam RT. The likelihood of ORN is related to the RT dose, volume of mandible irradiated, baseline dental status, and whether pre-RT or post-RT teeth extractions are required. Other parameters that may impact the likelihood of ORN include the timing of teeth extractions, primary site, body mass index, and bone surgery. ORN may be associated with significant morbidity and is difficult to manage so minimizing the risk is essential.

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