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Parameters Associated With Mandibular Osteoradionecrosis

William M. Mendenhall, MD,* Carlos Suárez, MD, PhD,†‡ Eric M. Genden, MD,§ Remco de Bree, MD, PhD, Primož Strojanič, MD, PhD,¶ Johannes A. Langendijk, MD, PhD,# Annti A. Makitie, MD, PhD,** Robert Smee, MB, BS, FRANZ,† Avraham Eisbruch, MD,‡‡ Anne W.M. Lee, MD, FCR, FHKCR, FHKAM,§§ Alessandra Rinaldo, MD, FRCS Ed ad hominem, FRCs (Eng, Ir) ad eundem, FRCS (Glasg) and Alféo Ferlito, MD, DLO, DPTh, FRCS Ed (Eng, Glasg, Ir) ad eundem, FDSRCS ad eundem, FACS, FHKCORL, FRCPath, FASCP, IFCAP

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. 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 scheme 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

From the *Department of Radiation Oncology, University of Florida College of Medicine, Gainesville, FL; †Health Research Institute of the Principality of Asturias and CIBERONC, ISCIII; ‡University Institute of Oncology of the Principality of Asturias University of Oviedo, Oviedo, Spain; §Department of Otolaryngology—Head and Neck Surgery, Icahn School of Medicine at Mount Sinai, New York, NY; ‖Department of Head and Neck Surgical Oncology, UMC Utrecht Cancer Center, University Medical Center Utrecht, Utrecht; ‡‡Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; †§Department of Radiation Oncology, Institute of Oncology, Ljubljana, Slovenia; **Department of Otorhinolaryngology—Head and Neck Surgery, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; †‡Department of Radiation Oncology, The Prince of Wales Cancer Centre, Sydney, NSW, Australia; †§Department of Radiation Oncology, University of Michigan, Ann Arbor, ME; §§Center of Clinical Oncology, University of Hong Kong—Shenzhen Hospital, Shenzhen, China; ‖‖Department of Otolaryngology, University of Udine School of Medicine; and §§International Head and Neck Scientific Group, Udine, Italy.

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Reprints: William M. Mendenhall, MD, 2000 SW Archer Rd, PO Box 100385, Gainesville, FL 32610-0385. E-mail: mendenw@shands.ufl.edu.

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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. 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 al15 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 al16 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 al17 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.5,18–20 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 al20 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 flutamide or postoperative RT between 1990 and 2000; the median RT to ORN was 6 months. The percentage of patients with mandibular ORN was 61%. 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.5,18–20 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.

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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 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 ($P = 0.0054$); one-day fractionation ($P = 0.0004$); brachytherapy boost ($P = 0.0002$); and pre-RT extractions ($P = 0.00154$).

Schuurbuis et al 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 peritreatment therapy (33%) rather than removal of these teeth (14%) emphasizing the importance of aggressive preventive strategies.

Goldwaser et al 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 reported on 1575 patients who had received RT for head and neck cancer and were evaluated in the Department 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 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 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, periodically dis- eased, 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 dose was reduced 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, 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,

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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 periodontal disease, and loss of opposing teeth and consequent loss of function of the opposing mandible. 


**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.

**REFERENCES**


