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Incidence of, and risk factors for, mandibular osteoradionecrosis in patients with oral cavity and oropharynx cancers

Dominic H. Moon [a], Sung Ho Moon [b], Kyle Wang [a], Mark C. Weissler [c], Trevor G. Hackman [c], Adam M. Zanation [c], Brian D. Thorp [c], Samip N. Patel [c], Jose P. Zevallos [c], Lawrence B. Marks [a], Bhishamjit S. Chera [a,*]

[a] Department of Radiation Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States
[b] Department of Radiation Oncology, Research Institute and Hospital, National Cancer Center, Goyang, South Korea
[c] Department of Otolaryngology/Head and Neck Surgery, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

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ABSTRACT

Objectives: To evaluate the incidence of, and risk factors associated with, mandibular osteoradionecrosis (MORN) following radiation therapy (RT) for oral cavity and oropharyngeal cancers.
Materials and Methods: Patient and treatment records of 252 consecutive patients with oral cavity or oropharynx cancers treated with RT by a single radiation oncologist at a high volume academic institution from August 2009 to December 2015 were retrospectively reviewed. A Cox regression model was used to assess factors associated with the development of MORN. RT dosimetry was compared between patients with MORN and a matched cohort of patients without MORN.
Results: MORN developed in 14 patients (5.5%), occurring 3–40 (median 8) months post-RT. Factors associated with MORN on univariable analysis included primary diagnosis of oral cavity vs oropharynx cancer (hazard ratio [HR]: 3.0, p = 0.04), smoking at the time of RT (HR: 3.1, p = 0.04), mandibular invasion of the primary (HR: 3.7, p = 0.04), pre-RT tooth extraction (HR: 4.52, p = 0.01), and treatment with 3D-conformal RT vs intensity-modulated RT (HR: 5.1, p = 0.003). On multivariable analysis, pre-RT tooth extractions and RT technique remained significant. A dosimetric comparison between patients with and without MORN showed no significant differences.
Conclusions and Relevance: The incidence of MORN is low in the modern era at a high volume academic center. Modifiable risk factors including pre-RT tooth extractions, smoking, and RT technique are associated with MORN, and the risk should be minimized with appropriate dental evaluation and treatment, smoking cessation efforts, and the use of intensity-modulated RT.

Introduction

Mandibular osteoradionecrosis (MORN) is a cause of significant morbidity in patients with head and neck cancers treated with radiation therapy (RT). Osteoradionecrosis is defined as an area of exposed bone secondary to necrosis following RT with failure to heal after a period of 3–6 months [1]. The mandible is the most commonly affected bone due to the distribution of head and neck primaries and the relative hypovascular nature of the mandible. The pathogenesis of MORN is thought to be secondary to bone tissue and vascular damage causing a hypoxic, hypocellular, and hypovascular environment [2] and a radiation-induced fibroatrophic process [3].

The reported incidence of MORN has decreased in recent years. The rate of MORN has declined from approximately 20% several decades ago [4,5] to 4–8% in modern series [6–9] with one series reporting no cases in a cohort of 176 patients at a median follow-up of 34 months [10]. This consistent decline in the incidence of MORN is attributed to the advances in RT technique and possible improvement in recognizing and mitigating risk factors.

Multiple risk factors have been associated with the development of MORN. These include tumor-related factors (tumor location, size, stage, presence of bone invasion), treatment-related factors (total RT dose, RT technique, volume of mandible irradiated), and patient-related factors (tobacco/alcohol use, oral hygiene, dental extractions, comorbidities) [6–9,11–14]. The variability in results

* Corresponding author at: Department of Radiation Oncology, University of North Carolina Hospitals, 101 Manning Drive, CB #7512, Chapel Hill, NC 27599-7512, United States.
E-mail address: bchera@med.unc.edu (B.S. Chera).

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from different series likely reflects a diverse patient population and RT techniques studied.

The primary objective of this study was to evaluate the incidence of MORN in patients with oral cavity cancers (OCC) and oropharyngeal cancers (OPC) treated by a single radiation oncologist at a high volume tertiary institution with a multidisciplinary head and neck oncology program. We also sought to examine and verify the potential risk factors associated with MORN.

Materials and methods

Patients

All patients with OCC and OPC treated with RT by a single radiation oncologist at a high volume tertiary academic institution between August 2009 and December 2015 were retrospectively reviewed. Patients receiving RT dose less than 60 Gy in 2-Gy fractions (or its equivalent using biological effective dose calculation for late effect) or re-irradiation, and those with less than 6 months of follow-up were excluded (except if MORN occurred prior to 6 months). Patient's demographics, social history including smoking and alcohol use, tumor characteristics, and treatment information were analyzed. Patients with MORN were identified based on the definition of clinically exposed mandibular bone secondary to necrosis following RT not related to progression of disease with failure to heal after a period of 3 months. Schwartz and Kagan classification system was used to stage the MORN [15].

Treatment

OPC patients received 60–70 Gy, depending on enrollment on a de-intensification protocol, which mandated a definitive dose of 60 Gy, with elective nodal RT dose to 50–54 Gy. OCC patients receiving post-operative RT received 60–66 Gy with elective nodal RT dose to 50–54 Gy. All patients received RT in 2-Gy fractions with the exception of 3 patients receiving 2.2 Gy/fraction and 4 patients receiving 1.2 Gy/fraction twice daily. Patients were predominantly treated with intensity-modulated radiation therapy (IMRT) with a subset receiving 3-dimensional conformal RT (3D-CRT), and received concurrent chemotherapy as appropriate. Patients underwent a pre-RT dental evaluation and management including tooth extractions as deemed appropriate by the radiation oncologist and/or dentist based on risk assessment.

Statistical analysis

Chi-squared test was used to compare patient and treatment characteristics of patients with and without MORN. A univariable Cox regression model was used to assess patient and treatment factors associated with the development of MORN. In addition, a multivariable Cox regression was performed with two covariates per analysis.

A matched, nested case-control analysis was done to evaluate the dosimetry to the mandible. One patient without MORN was matched to each of the 14 patients with MORN (i.e. 1:1 matching) by RT type (3D-CRT vs IMRT), status of pre-RT tooth extraction, primary site (OCC vs OPC), smoking status, and the presence of mandibular invasion (all potential risk factors for MORN). When feasible, the patient's age, sex, and treatment period were also matched. Dosimetric data for the mandible analyzed included maximum dose to the mandible (D_{max}), mean mandibular dose (D_{mean}), and the percent volume of mandible receiving 40 Gy (V40), 50 Gy (V50), 60 Gy (V60), and 70 Gy (V70). Dosimetry of patients between those with and without MORN and those who received 3D-CRT vs IMRT were compared using the Mann-Whitney test with two tails. P-values of < 0.05 were considered statistically significant. All statistical analyses were conducted using SPSS (IBM SPSS Statistics, version 21.0, New York, United States).

Results

Patient and treatment characteristics

Of the 282 eligible patients, 30 were excluded based on the exclusion criteria, leaving 252 patients for analysis with a median follow-up of 25 months (range: 6–81 months). Patient and treatment characteristics are summarized in Table 1. In this cohort, most patients had OPC (73%), were treated with IMRT (89%), and received concurrent chemotherapy with RT (85%). Mandibular surgery including mandibulotomy, partial, segmental, and hemimandibulectomy were performed in 31% of the OCC patients. Median, mean, and range of RT doses delivered were 70 Gy, 66.3 Gy, and 60 Gy–74.4 Gy, respectively.

Incidence of mandibular osteoradionecrosis

MORN developed in 14 patients (5.5%) with a median time to developing MORN of 8 months (range: 3–40 months). Patient and treatment characteristics of those with and without MORN are summarized in Table 1. The rate of MORN was higher in current smokers vs non-smokers (11% vs 3.4%, $p = 0.032$), patients receiving pre-RT tooth extraction vs those who did not (11% vs 2.4%), and patients treated with 3D-CRT vs IMRT (19% vs 4.0%, $p = 0.01$). Details of 14 patients who developed MORN are summarized in Table 2. MORN developed spontaneously without an associated procedure or trauma in 11 of 14 patients (79%). The majority had stage 1–2 MORN by Schwartz and Kagan classification with stage 3 MORN developing in 5 patients (overall incidence of 2.0%). Three patients (21%) required surgical management, 3 additional patients (21%) received hyperbaric oxygen therapy, and the rest were managed conservatively. At the time of analysis, 11 of 14 patients (79%) had either a resolution or stabilization of their MORN.

Risk factors associated with the development of mandibular osteoradionecrosis

Factors associated with MORN on univariable analysis included primary diagnosis of OCC vs OPC (Hazard ratio [HR]: 3.0, $p = 0.04$), smoking at the time of RT (HR: 3.1, $p = 0.04$), mandibular invasion of the primary (HR: 3.7, $p = 0.04$), pre-RT tooth extraction (HR: 4.52, $p = 0.01$), and treatment with 3D-CRT vs IMRT (HR: 5.1, $p = 0.003$) (Table 3). On multivariable analysis of two covariates per analysis, RT technique remained significant when accounting for pre-RT tooth extraction and smoking status. Pre-RT tooth extraction was also significant when accounting for all other covariates in pairs. The site of the primary, mandibular invasion, and smoking status fell out of statistical significance on multivariable analysis.

Dosimetry of patients with and without mandibular osteoradionecrosis

Among the 14 patients with MORN, the mean D_{mean}, D_{max}, V40, V50, V60, and V70 were 49.0 Gy, 71.7 Gy, 69%, 61%, 45%, and 17%, respectively (Table 4). There was no significant difference in the dosimetry when compared to a nested cohort of patients without MORN matched for the factors associated with MORN on univariable analysis (primary diagnosis, smoking status, mandibular invasion, pre-RT tooth extraction, and RT treatment modality). Among