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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

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ABSTRACT

Objective: To determine the prevalence and correlation of various risk factors [radiation dose, periodontal status, alcohol and smoking] to the development of osteoradionecrosis (ORN).
Patients and methods: The records of 1023 patients treated with IMRT for oral cavity cancer (OCC) and oropharyngeal cancer (OPC) between 2004 and 2013 were retrospectively reviewed to identify patients who developed ORN. Fisher exact tests were used to analyze patient characteristics between ORN patients with OCC and OPC. Paired Wilcoxon tests were used to compare the dose volumes to the ORN and contralateral non-ORN sites. To evaluate an association between ORN and risk factors, a case-control comparison was performed. One to 2 ORN-free patients were selected to match each ORN patient by gender, tumor site and size. General estimation equations models were used to compare the risk factors in ORN cases and matched controls.
Results: 44 (4.3%) patients developed ORN during a median follow-up time of 52.5 months. In 82% of patients, ORN occurred spontaneously. Patients with OPC are prone to develop ORN earlier compared to patients with OCC ($P = 0.03$). OPC patients received a higher Dmax compared to OCC patients ($P = 0.01$). In the matched case-control analysis the significant risk factors on univariate analysis were poor periodontal status, history of alcohol use and radiation dose ($P = 0.03$, 0.002 and 0.009, respectively) and on multivariate analysis were alcohol use and radiation dose ($P = 0.004$ and 0.026, respectively).
Conclusion: In our study, higher radiation dose, poor periodontal status and alcohol use are significantly related to the risk of developing ORN.

Introduction

Osteoradionecrosis (ORN) of the jaw is a well-known complication of radiation therapy to the head and neck. ORN is defined as an area of exposed necrotic bone in an area previously irradiated that fails to heal over a period of 3–6 months. However, cases with radiographic evidence of necrosis with intact mucosa have been described [1–5].

Head and neck cancers are sensitive to radiotherapy (RT), which is being increasingly used with the rising prevalence of human papilloma virus positive squamous cell carcinoma. The treatment mainstay in these cases remains radiation therapy alone or in combination with chemotherapy [6,7]. Since the advent of intensity-modulated radiation therapy (IMRT) in the treatment of head and neck cancer, the associated co-morbidities of radiation therapy have been minimized by limiting radiation exposure to healthy

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tissue and maximizing loco-regional tumor control [8–10]. Earlier studies looking at the rate of ORN in patients treated in the era of IMRT have reported a reduced prevalence compared to patients treated with conventional radiotherapy [11–14].

Various risk factors have been suggested to be associated with the development of ORN. The local risk factors include tumor site, tumor stage, proximity of the tumor to bone, radiation field, dose of radiation, poor oral hygiene, and associated trauma, such as dental extraction/surgery before or after RT. Systemic factors include co-morbidities, smoking and drinking alcohol, immunodeficient status, and infection [15–20]. The aims of this study are: (1) to report the current prevalence of ORN in patients with oral cavity cancer (OCC) and oropharyngeal cancer (OPC) treated with IMRT between 2004 and 2013 in our institution; and (2) to evaluate the correlation between various risk factors [radiation dose, periodontal status, alcohol and smoking] and the development of ORN.

Patients and methods

Patients

This retrospective study was approved by Memorial Sloan Kettering Cancer Center's (MSKCC) Institutional Review Board. We reviewed the records of all oral cavity cancer (OCC) and oropharyngeal cancer (OPC) patients treated with IMRT in our institution between 2004 and 2013 to identify patients who developed ORN. ORN is defined as either clinically exposed necrotic bone that failed to heal over a period of 3 months or patients with radiographic evidence of necrosis with intact mucosa. The following clinical information was reviewed: demographic data, tumor site, tumor diagnosis, tumor stage, and radiation dose to the primary tumor, dental events, ORN stage, social history (alcohol and smoking history), history of diabetes mellitus, follow-up data, and management of patients who developed ORN.

Radiation treatment

All patients with oral and oropharyngeal cancer diagnosed during the period of 2004–2013 were treated with IMRT using a dose-painting technique. All areas of gross disease received 66–70 Gy and regions of elective nodal radiation received 50–60 Gy. Uninvolved low anterior neck received 45–50 Gy. For patients receiving postoperative radiation, the dose to the surgical bed dose was typically 60 Gy.

Follow-up period

The follow-up period was calculated from the completion of RT to the patient's last clinical visit with MSKCC's Department of Radiation Oncology or Dental Service. Follow-up was calculated up until July 31, 2016. The follow-up period for all patients spans 4–140 months with a median time of 52.5 months. The time from completion of RT to ORN diagnosis was also noted.

ORN definition and grading

ORN is an area of clinically exposed necrotic bone that failed to heal over a period of 3–6 months in an area previously irradiated. However, there is a subset of ORN that presents with clinically intact mucosa along with radiographic evidence of bone loss [3–5]. We included both subsets in our cohort. For the sake of consistency with the literature we adopted a modified version of the Glanzmann and Graetz grading system [21].

The ORN grading (adopted modified Glanzmann and Graetz grading) used is as follows:

0 – Radiographic ORN with intact mucosa.
1 – Exposed necrotic bone without signs of infection for at least 3 months.
2 – Exposed necrotic bone with signs of infection or sequestrum, but not grades 3–4.
3 – ORN resulting to pathologic fracture or ORN treated with surgical resection, with satisfactory result.
4 – ORN refractory to surgical resection.

Dosimetry of ORN site, contralateral non-ORN site and statistical analysis

Using the MSKCC radiation treatment planning software, the mean (Dmean) and maximum point radiation doses (Dmax) of the ORN region and contralateral non-ORN region of the jaw were calculated via dosimetric contour as previously described [22]. A case-control comparison was performed with one to two ORN-free patients selected to match each ORN patient by gender, primary tumor site and size. Statistical analysis was performed using generalized estimating equation logistic regression to compare the risk factors (radiation dose, pre-RT periodontal status, alcohol and smoking post-RT history) in ORN cases and matched controls. Fisher exact tests were used to analyze patient characteristics between ORN patients with oral cavity cancer (OCC) and oropharyngeal cancer (OPC). Paired Wilcoxon tests were used to compare the dose volumes (Dmean and Dmax) to the ORN and contralateral non-ORN sites in patients who developed ORN unilaterally.

Dental evaluation and management of ORN

Patients referred to the Dental Service of MSKCC prior to radiation therapy underwent comprehensive clinical and radiographic evaluation and dental intervention if indicated. Pre-radiation whole-mouth saliva and inter-incisal opening measurements were obtained. Radiation mouth guards were fabricated for patients to help reduce the dose and toxicity from backscatters in patients with significant metal dental restorations. All patients were prescribed aggressive fluoride regimen. Patients were evaluated at mid-RT, and at various time points post-RT.

Conservative management through close observation, prescription of 0.12% chlorhexidine rinse for local debridement, antibiotics (typically, Augmentin 875 mg BID) and pain medication when indicated were utilized. Subsequently, if the exposed necrotic bone becomes increasingly mobile, the sequestrum was passively removed [treatment option I]. Pentoxifylline 400 mg and tocopherol 400 IU BID were prescribed to some patients in combination with 0.12% chlorhexidine rinse for local debridement [treatment option II]. Segmental mandibulectomy was employed after all other treatment options failed and the lesions progressed to involve the basal bone of the mandible and/or had a pathologic fracture [treatment option III]. Hyperbaric oxygen was instituted in one patient for management of ORN [treatment option IV]. Outcomes of management were assessed in four categories: complete resolution (complete mucosal coverage of prior exposed bone), partial resolution (reduction in size of exposed bone), no resolution and progression (increase in size of exposed bone).

Results

Clinical analysis and prevalence

Between January 2004 and December 2013, 1023 oral cavity (OCC; n = 299) cancer and oropharyngeal cancer (OPC; n = 724) patients were treated with IMRT in our institution. The medical and dental records of all 1023 patients were reviewed. Forty-four