Osteoradionecrosis following treatment for head and neck cancer and the effect of radiotherapy dosimetry: the Guy's and St Thomas' Head and Neck Cancer Unit experience

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Objectives. To analyze clinical features, dosimetric parameters, and outcomes of osteoradionecrosis (ORN).
Study Design. Thirty-six patients with ORN who had been previously treated with radiotherapy (RT) were retrospectively identified between January 2009 and April 2014. ORN volumes were contoured on planning computed tomography (CT) scans. Near maximum dose (D2%), minimum dose (Dmin), mean dose (Dmean), and percentage of bone volume receiving 50 Gy (V50) were examined. Clinical and dosimetric variables were considered to compare ORN resolution versus ORN persistence.
Results. Median interval time from end of RT to development of ORN was 6 months. Of the ORN cases, 61% were located in the mandible. Dmean to affected bone was 57.6 Gy, and 44% had a D2% 65 Gy or greater. Smoking was associated with ORN persistence on univariate analysis, but no factors were found to impact ORN resolution or progression on logistic regression.
Conclusions. Prevention strategies for ORN development should be prioritized. Dose-volume parameters could have a role in preventing ORN. (Oral Surg Oral Med Oral Pathol Oral Radiol 2016;122:28-34)

Head and neck cancer (HNC), with 9127 estimated new cases per year, is a relatively rare carcinoma in the United Kingdom.[1] The approach to treatment is complex and depends on the site and stage of the primary tumor. It often involves multimodality treatment, including surgery, radiation therapy (RT), and chemotherapy in advanced cases, whereas early-stage disease can be treated with single-modality treatment, surgery, or RT.[2]

Osteoradionecrosis (ORN) remains one of the most severe complications of RT for HNC, but in the intensity-modulated RT (IMRT) era, it has become a rare condition, affecting up to 6.4% of patients.[3-12] Radiation factors, including total dose, daily fraction size, and irradiated volume, play an important role in the ORN process. Generally, the mandible is the bone in the head and neck region at highest risk of developing ORN. Radiation area could occlude the inferior alveolar artery, causing premature atherosclerosis, adventitial fibrosis, and necrosis, of the arterial wall; consequently, hypoxia and hypocellularity contribute to ischemic necrosis in the irradiated atrophic tissue.[13-15]

The aim of this study was to retrospectively review patients who were diagnosed with ORN and treated for HNC at our Institution and to investigate the clinical features, dosimetric parameters, and outcome of these patients. We also analyzed the potential risk factors related to ORN persistence.

MATERIALS AND METHODS

Patient population

Data of patients with ORN treated for primary HNC between January 2009 and April 2014 were retrospectively reviewed. All cases were discussed in a meeting of a multidisciplinary team, including clinical oncologists, surgeons, dentists, radiologists, and pathologists. For all cases demographic data (including gender, age, smoking, alcohol, performance status), primary tumor parameters (i.e., localization, tumor stage, treatment modality, toxicity) and dental assessment documentation (time and localization of any dental extraction) were obtained.

Primary treatment

All patients received RT, delivered with a three-dimensional (3-D) conformal technique until June 2010 and IMRT, which was forward planned until May 2011 and inverse planned thereafter. The high-dose clinical

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target volume (CTV) consisted of the primary tumor and the involved lymph nodes, as well as the entire organ where the tumor arose and the structures at risk for microscopic tumor spread. Prescribed doses were 65 to 70 Gy in 30 to 35 daily fractions. For postoperative treatments, high-dose CTV included the surgical tumor bed, and the doses were 60 to 66 Gy in 30 to 33 fractions. The low-dose CTV was defined to receive a prophylactic dose of 50 to 54 Gy in 25 to 30 fractions and delineated according to the European Organization for Research and Treatment of Cancer (EORTC) consensus guidelines.[16-18] A planning target volume (PTV) was created, adding a margin of 4 mm to each CTV.

Concomitant platinum-based chemotherapy was recommended in stage III and IV disease treated with primary RT and in postoperative cases where positive surgical margins and/or extracapsular nodal spread were observed. Induction chemotherapy was used in patients with bulky disease.

Follow-up was obtained from medical records and included survival outcomes and ORN detection.

Osteoradionecrosis

ORN was defined as exposure of bone for more than 3 months[19] or radiologic evidence without breach of the oral mucosa or cervicofacial skin[20] and graded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE, US Department of Health and Human Services)[21] and the Lyons et al. classification[20] (Table I). ORN was diagnosed on the basis of clinical features and symptoms. Tumor failures were excluded through pathologic findings.

Conservative treatment included pentoxifylline 400 mg twice a day and tocopherol 1000 IU units once a day for between 1 and 24 months. Surgical management consisted of bone resection with or without tissue reconstruction.

ORN was considered resolved in case of soft tissue coverage of bone and absence of pain.

Dosimetric evaluation

Radiotherapy treatment plans are assessed by using dose-volume parameters that reflect target volume objectives and organs at risk (OARs) constraints to ensure that the tumor is covered by the prescribed radiation dose and that normal tissues are not overdosed. This is particularly relevant to IMRT plans because it allows a more conformal delivery to the tumor and sparing of OARs. These parameters include the near maximum dose (D2%), the minimum dose (Dmin), the mean dose (Dmean), and the percentage of the volume receiving "x" Gy (Vx). For OARs such as bone/mandible, both the D2% received and the partial dose or volume parameters are potentially the most relevant.

Table I. Osteoradionecrosis (ORN) grading

Common terminology criteria for adverse events[21]	
Grade of ORN	*Definition*
1	Asymptomatic; clinical or diagnostic observations only
2	Symptomatic; medical intervention indicated (topical agents); limiting instrumental activities of daily living (ADLs)
3	Severe symptoms; limiting self-care ADLs; elective operative intervention indicated
4	Life-threatening consequences; urgent intervention indicated
Lyons et al. ORN grading scale[20]	
Grade of ORN	*Definition*
1	<2.5 cm length of bone affected (damaged or exposed); asymptomatic; medical treatment only
2	>2.5 cm length of bone; asymptomatic, including pathologic fracture or involvement of inferior dental nerve or both Medical treatment only unless there is dental sepsis or obviously loose necrotic bone
3	>2.5 cm length of bone; symptomatic, but with no other features despite medical treatment Consider debridement of loose or necrotic bone, and local pedicle flap
4	2.5 cm length of bone; pathologic fracture, involvement of inferior dental nerve, or orocutaneous fistula, or a combination Reconstruction with free flap if patient's overall condition allows

ADL, Activities of daily living.

For the purpose of the study, original treatment plans were reviewed. Contouring of the ORN volume was performed on the basis of evaluation of orthopanoramic radiography and/or CT with contrast, in collaboration with a radiologist with specialization in the head and neck region and a dental surgeon. The mandibular dose distribution was recalculated, as well as dose-volume histograms (DVHs). For each ORN volume the D2%, the Dmin, the Dmean were considered. In case of mandible localization, the percentage of volume mandible receiving 50 Gy (V50) was also considered.

Statistical analysis

Statistical analysis was performed by using RStudio-0.98.1091 software (RStudio Inc., Boston, MA). Standard descriptive statistics were used to evaluate the distribution of each potential factor. DVHs were evaluated, and the following predictive factors were considered as variables: age, smoking and alcohol consumption, treatment modality and related toxicity, dental extractions, and RT doses to ORN volume. To determine the association between ORN resolution and predictive factors, a univariate analysis was performed using the Fisher's test. Logistic regression was used to