LACK OF OSTEORADIONECROSIS OF THE MANDIBLE AFTER INTENSITY-MODULATED RADIOTHERAPY FOR HEAD AND NECK CANCER: LIKELY CONTRIBUTIONS OF BOTH DENTAL CARE AND IMPROVED DOSE DISTRIBUTIONS


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Purpose: To assess the prevalence and dosimetric and clinical predictors of mandibular osteoradionecrosis (ORN) in patients with head and neck cancer who underwent a pretherapy dental evaluation and prophylactic treatment according to a uniform policy and were treated with intensity-modulated radiotherapy (IMRT).

Methods and Materials: Between 1996 and 2005, all patients with head-and-neck cancer treated with parotid gland-sparing IMRT in prospective studies underwent a dental examination and prophylactic treatment according to a uniform policy that included extractions of high-risk, periodontally involved, and nonrestorable teeth in parts of the mandible expected to receive high radiation doses, fluoride supplements, and the placement of guards aiming to reduce electron backscatter off metal teeth restorations. The IMRT plans included dose constraints for the maximal mandibular doses and reduced mean parotid gland and noninvolved oral cavity doses. A retrospective analysis of Grade 2 or worse (clinical) ORN was performed.

Results: A total of 176 patients had a minimal follow-up of 6 months. Of these, 31 (17%) had undergone teeth extractions before RT and 13 (7%) after RT. Of the 176 patients, 75% and 50% had received >65 Gy and >70 Gy to ≥1% of the mandibular volume, respectively. Falloff across the mandible characterized the dose distributions: the average gradient (in the axial plane containing the maximal mandibular dose) was 11 Gy (range, 1–27 Gy; median, 8 Gy). At a median follow-up of 34 months, no cases of ORN had developed (95% confidence interval, 0 – 2%).

Conclusion: The use of a strict prophylactic dental care policy and IMRT resulted in no case of clinical ORN. In addition to the dosimetric advantages offered by IMRT, meticulous dental prophylactic care is likely an essential factor in reducing ORN risk. © 2007 Elsevier Inc.

Intensity-modulated radiotherapy, Osteoradionecrosis, Head and neck cancer.

INTRODUCTION

Osteoradionecrosis (ORN) of the mandibular bone is a well-documented complication of radiotherapy (RT) for head-and-neck cancer (1–4). Generally, bones are resistant to high radiation doses and will not sustain any overt damage as long as the overlying soft tissue remains intact and the bone is not subjected to excessive stress or trauma. Mendenhall (3) recently noted that the presentation of ORN after RT varies from small, asymptomatic bone exposures that can remain stable for months or years or heal with conservative management to severe necrosis necessitating surgical intervention and reconstruction. Several risk factors are associated with the development of ORN, including age, gender, general health, primary tumor site and stage, proximity of the tumor to bone or its invasion, dentition status, treatment type (e.g., external beam RT, brachytherapy, surgery, or chemotherapy or combinations), radiation dose, and associated trauma, such as teeth extraction before or after RT or surgery (1–3).

Since 1996, patients with head and neck cancer have been treated at the University of Michigan with intensity-modulated RT (IMRT) techniques primarily aimed at reducing the major salivary gland doses. In addition, they produced dose gradients across the mandible. During that period, all patients underwent a pre-RT dental evaluation and prophylactic care according to uniform policies. The original aim of this retrospective study was to compare the mandibular...
doses and clinical factors in patients receiving IMRT who did or did not develop ORN. However, because no ORN was found in any of these patients, we present the mandibular dose distributions and relevant clinical factors, especially those related to dental care, that may have contributed to the lack of this complication.

METHODS AND MATERIALS

Patients
The patients evaluated in this retrospective study received IMRT to the bilateral neck with curative intent, participated in prospective clinical protocols, had not received previous RT, and had ≥6 months of follow-up after RT completion. After institutional review board approval, their charts and treatment plans were reviewed.

Dental evaluation and treatment
Before RT, all patients underwent a dental evaluation at the Hospital Dentistry Clinic. During this consultation, the patient’s complete medical, dental, social, and family histories were obtained, and potential oral side effects of RT, including xerostomia, dental caries, ORN, mucositis, and trismus, were reviewed with the patient, and strategies for prevention were discussed. The examination included a tooth-by-tooth evaluation, with particular attention to the teeth in the parts of the jaws expected to receive a high dose (≥50 Gy). The periodontal condition was evaluated, and teeth with mobility, significant pocketing, furcation involvement, or advanced recession were recommended for extraction. All patients underwent panoramic radiographs, which were supplemented in some patients by intraoral periapical radiographs, if necessary, to evaluate for periapical abscesses, caries, and the periodontal condition. Teeth with nonrestorable caries or caries that extended to the gum line, teeth with large, compromised restorations with significant periodontal attachment loss (pocketing ≥5 mm), and those with severe erosion or abrasion were extracted if they were in the parts of the jaws expected to receive a high dose (the posterior mandible and maxilla ipsilateral to the tumor and the posterior mandible contralateral to the tumor). Teeth residing in the anterior mandible were not considered for extraction unless the primary tumor was in the oral cavity. Decisions about extraction were significantly affected by the patient’s competence and interest in performing meticulous oral hygiene and by the patient’s past history of dental service use. A more aggressive approach was made after surgical oral reconstructions that inhibit oral hygiene or in patients with trismus because of their negative impact on the prognosis for the teeth. Extractions were performed as soon as possible after examination, and primary closure was attempted when possible in the extraction sites. The residual alveolar ridges were prepared for dentures by performing any needed preprosthetic surgery such as alveoloplasty and torus removal. The start of RT was delayed by ≥14 days after extraction to allow for complete healing of the extraction site.

Patient education
Oral hygiene, including secular brushing and flossing, was reviewed with each patient. Daily use of high-concentrated fluoride gel (1.1% neutral sodium fluoride) either in a fluoride carrier or by brush-on technique was also recommended, and a prescription was given to the patient. Written information and instructions were provided, including oral care during and after RT, using the National Institute of Dental and Craniofacial Research (4) and in-house supplemental material.

Additional dental procedures
For all patients with dentitions heavily restored with metallic restorations, radiation guards were used (Fig. 1). These were made from polyvinyl siloxane putty (Reprosil, Caulk-Dentsply, York, PA) and were intended to provide a 5-mm separation between the metallic restorations and the soft tissue, with the intention of reducing electron backscatter off the metal onto the soft tissue. The base and catalyst of the putty were hand mixed and placed on posterior quadrant triple trays (Sullivan Schein, Melville, NY) and placed in the mouth. Four wooden tongue blades were placed between the upper and lower incisors, and the patient was asked to close the mouth until the tongue blades were snug between the anterior teeth. After a setting time of about 5 min, the guards were removed and disinfected. They were trimmed to achieve a 5 mm thickness. The silicone was polished using a satin wheel (E.C. Moore, Dearborn, MI) and delivered to the patient with instructions in use and care. The guards were in place during the simu-
lation to ensure that they were taken into account in the treatment planning dosimetry.

Radiotherapy

The target definition and radiation techniques have been detailed elsewhere (5–9). The planning target volumes (PTVs) were created by uniform expansion of the clinical target volumes by 0.5 cm. In recent years, the use of on-line imaging and daily correction of the systematic setup errors by the radiation therapists had been found to reduce the systematic errors to a mean ± SD of 1 ± 1.5 mm (unpublished data), and the PTV expansion has been reduced to 3 mm. Patients were treated until 2002 using static multisegmental IMRT (7, 8) and afterward by inverse-planned beamlet IMRT (9). The prescribed target dose was 70 Gy to the gross tumor PTV in 35 fractions, and low- and high-risk clinical target volumes were prescribed a dose of 56–64 Gy at 1.6–1.8-Gy fractions.

The optimization cost functions penalized the maximal mandibular dose (<72 Gy), mean parotid gland (±26 Gy), and mean noninvolved oral cavity dose (±30 Gy). The oral cavity structure included the mandible, buccal mucosa, tongue, base of tongue, floor of mouth and palate, and its delineation has previously been detailed (10). The noninvolved oral cavity was obtained by subtracting the PTVs from the oral cavity volume. In all patients, the plans strived to address the target prescription goals while reducing target dose inhomogeneity. In recent years, the planning goals also included reduced doses to the swallowing structures (11, 12).

For the purposes of this study, all available treatment plans were reviewed (148 plans, 84%). The mandibular dose distributions were recalculated, and their dose–volume histograms were generated again for all patients, using the edge/octree model calculation and the convolution/superposition model for patients treated with multisegmental IMRT and beamlet IMRT, respectively.

Follow-up

All patients were followed every 6–8 weeks during the first 2 years after therapy and every 3–4 months afterward in both the Radiation Oncology and the Head and Neck Surgery Clinics. Follow-up visits at the Hospital Dentistry/Oral Surgery Clinic were used when specific dental problems or suspected ORN were observed at the other clinics.

ORN definition

Several staging/grading systems have been suggested for ORN (2, 13, 14), taking into consideration the response to hyperbaric oxygen (HBO) (14), the presence of pathologic fractures (13), and the clinical presentation (2) or a combination of the above (15). We have elected to use the Common Terminology Criteria for Adverse Events, version 3.0 (15) for the grading of ORN in this series and to retrospectively assign a grade according to the clinical and radiographic findings detailed in the patients’ charts. The ORN definition and grading according to the Common Terminology Criteria for Adverse Events, version 3.0, is as follows: Grade 1, asymptomatic, radiographic findings only; Grade 2, symptomatic and interfering with function, minimal bone removal indicated; Grade 3, symptomatic and interfering with daily life activities, operative intervention or HBO indicated; and Grade 4, disabling. Because routine radiographs were not performed after therapy in most patients, we sought to identify those patients who had Grade 2 ORN or worse, defining Grade 2 as bony exposure observed for at least two follow-up clinic visits (i.e., persisting for ≥6–8 weeks). The follow-up notes from all clinics were reviewed for each patient to capture all possible cases of ORN.

RESULTS

Between March 1996 and March 2005, 188 patients were treated with IMRT in prospective trials. Of the 188 patients, 9 who had <6 months of follow-up (5 were lost to follow-up at <6 months, 2 had died of pneumonia or trauma, and 2 had died of lung metastases), and 3 patients who did not complete the RT course, were excluded from this analysis (none had ORN at last contact); thus, the total number of patients evaluated in this study was 176. The patient characteristics are summarized in Table 1. The large majority had oral or oropharyngeal primary tumors. All 20 patients with laryngeal or hypopharyngeal cancer presented with advanced neck lymphadenopathy and the posterior mandible was within, or close to, the lymphatic nodal targets. Of the 176 patients, 107 (61%) received primary RT and 69 (39%) received postoperative RT. Also, 108 patients were treated with concurrent chemotherapy: cisplatin based in 22 patients, carboplatin based in 44, and a combination of carboplatin and paclitaxel in 43 patients.

The pretherapy dental examination and treatment information were available for 174 patients (99%). Of these 174 patients, 16 (9%) were edentulous at presentation, and 6 (3%) had had all their remaining teeth extracted before RT. Of the 176 patients, 157 (89%) were dentulous during RT. Of the 157 dentulous patients, 30 (19%) had undergone pretherapy mandibular teeth extractions (median number of teeth removed, 2; range, 1–8). In almost all cases, the extractions were from the posterior parts of the mandible that were expected to receive high radiation doses. All other patients (122 patients, 69%) were cleared to start RT without extraction. Thirteen patients underwent post-RT mandibular teeth extractions at the University of Michigan Den-

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Abbreviation: American Joint Committee on Cancer.
tal Clinic. Six of these patients had teeth extracted from the parts of the mandible that had received a maximal dose >60 Gy, two of these patients had received HBO before the procedure. Seven other patients had teeth extracted from the parts of the mandible that had received lower maximal doses. The median follow-up after the extractions in these patients was 26 months. Some patients elected to proceed with post-therapy dental follow-up with their local dentist; therefore, the information regarding any post-RT extractions was not available for all patients.

The mandibular dose–volume histograms generated for all available treatment plans are summarized in Fig. 2. The mean ± SD V50, V60, and V70 (percent volumes receiving 50 Gy, 60 Gy, and 70 Gy, respectively) was 62% ± 18%, 35% ± 20%, and 6.5% ± 5%, respectively. No significant differences were found in the dose–volume histogram parameters between patients treated with multisegmental or beamlet IMRT. The highest doses to ≥1% of the volume of the mandible are summarized in Fig. 3. The mean mandibular volume was 58.8 ± 14.4 cm³, such that, on average, a 1% volume represented 0.59 cm³. More than 75% and 50% of the patients had a maximal dose of ≥65 Gy and 70 Gy to ≥1% of the mandibular volume, respectively. The treatment plans were characterized by dose gradients across the mandible. The average gradient across the mandibular bone, in an axial plane that included the maximal dose, was 11 Gy (range, 1–27 Gy; median, 8 Gy). Figure 4 is of a patient treated with IMRT for Stage T3N1 squamous cell carcinoma of the right tonsil and posterior pharyngeal wall. The primary PTV prescribed dose was 70 Gy, and the dose falloff across the mandible, perpendicular to the maximal dose delivered to the inner mandibular plate adjoining the PTV, was 21 Gy (72 Gy through 51 Gy).

Dosimetry of the major salivary glands showed that the mean doses to the contralateral and ipsilateral submandibular glands were, on average, 57 ± 8 Gy and 65 ± 7 Gy, respectively. These doses resulted in significant sparing of the salivary flows from the contralateral parotid glands, which increased continuously during the first 2 years after therapy completion, as well as in improvements over time in patient-reported xerostomia. The results of the sialometry and xerostomia-related symptoms in the patients participating in this study have been previously published (10, 16–18).

The median follow-up was 35 months (range, 6–129 months). Of the 148 patients still alive, 124 (70%) had at least 2 years, 82 (55%) had at least 3 years, and 47 (32%) had at least 5 years of follow-up.

Twenty-seven patients (15%) developed locoregional disease recurrence. Of these 27 patients, 4 also had lung disease, and 4 had metastatic disease only.

No case with ORN was identified (95% confidence interval, 0–2%). One patient had a clinical suspicion of ORN because of local pain; however, no mandibular bone exposure was observed and a panoramic X-ray demonstrated no bone changes. One patient had asymptomatic transient mandibular bone exposure diagnosed during routine clinical examination, but a panoramic X-ray of the jaws demonstrated no bone changes.

DISCUSSION

The incidence of ORN after RT for head-and-neck cancer has declined in recent decades, from 11.8% before 1968 to 5.4% from 1968 to 1992, and decreased again after 1997 to approximately 3% (1). The reduction in the incidence of ORN occurred despite an increasing intensity of therapy in recent years, such as concurrent chemo-RT and altered fractionated RT, which are characterized by increased acute side effects of therapy and occasionally by increased rates of late sequelae (19, 20). The recent reduction in ORN risk is reflected in our series, in which no case was observed among 176 patients, with a 95% confidence interval of 0–2% (indicating that we cannot exclude a rate of ORN of ≤2% in patient populations similar to the sample we have studied). ORN is a late sequel and some cases may require long follow-up; however, the large majority of events have
been reported to occur within 2 years after therapy (21). The low risk found in our series, in which 70% of patients were followed for ≥2 years, was likely not related to a short follow-up. The reduction in the ORN rates can be attributed to the more conformal dose distributions, which spared parts of the mandible that would have received a high dose had conventional techniques been used, and to better prophylactic and on-going dental care. Of these two factors, dosimetric improvements and better dental care, it remains to be determined which is the most important.

Although some patients in our series received a high maximal dose to the mandible, with one-half receiving ≥70 Gy, the mandibular volumes receiving a high dose were small (on average, the V70 was 6.5%, which translates to about 4 cm³ of an average mandibular volume of 60 cm³). Smaller volumes receiving high doses might have reduced the risk of bony exposure resulting from severe acute mucositis and leading to consequential long-term damage. In addition to limiting the mandibular volumes receiving a high dose, the dose distributions in this series were characterized by a falloff across the mandible, with the outer plate of the mandible across the “hot spot” receiving a lower dose. This dose falloff might have implications regarding long-term effects on the local blood supply and the bone’s ability to withstand future trauma such as teeth extractions. Not only has the total dose been limited, but in patients receiving a single IMRT plan, the reduced total doses translated into reduced fraction doses, such that the biologically equivalent doses delivered to the parts of the mandible receiving <70 Gy were lower than their nominal doses would imply. For example, in a patient with a maximal mandibular dose of 70 Gy delivered to the inner mandibular plate and a gradient of 11 Gy across the mandible (the average gradient in our series), delivered within 35 fractions, the nominal dose to the outer mandibular plate was 59 Gy delivered at 1.68 Gy/fraction. This is thought to be biologically equivalent to 55 Gy at 2 Gy/fraction, assuming a low α/β ratio for late effects. In contrast, in a patient with oral or oropharyngeal cancer treated with conventional RT in which the final boost is delivered to the gross disease using lateral opposed fields, the volume of the mandible receiving 70 Gy is expected to be much greater, with the high dose delivered to the full thickness of the mandible at the same dose fraction prescribed to the tumor.

Parliament et al. (22) examined the mandibular dose distributions in a few IMRT cases and compared them with those of standard RT. They concluded that IMRT offers a dosimetric advantage if sparing the mandible is included in the plan optimization (22). In our series, reducing the mandibular doses was achieved by constraints on the maximal dose to the mandible and the mean dose to the noninvolved oral cavity (which encompassed the mandible). The mean dose constraint for the oral cavity was achieved by constraints on the maximal dose to the mandible and the mean dose to the noninvolved oral cavity (which encompassed the mandible). The mean dose constraint for the oral cavity was enacted to reduce ORN risk and mucositis, as well as xerostomia, which was found in an earlier study to be affected by the mean oral cavity dose (which represented the potential damage to the minor salivary glands) (10). In addition to reduced mandibular doses, the partial sparing of the salivary output achieved by IMRT might have reduced the ORN risk through reduced teeth decay, a consequence of hyposalivation (23).

A clinical series concentrating on ORN in patients receiving IMRT has recently been reported by Studer et al. (24) In
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This series, detailed dosimetry of the mandible showed small bone volumes receiving high doses, similar to our experience, and only 1 of 73 patients developed ORN. Other clinical series of IMRT for head and neck cancer have reported a very low incidence of ORN (25), and others did not include ORN as one of their late complications. It is not clear whether no cases were observed or ORN was not recorded in these series (26–29). However, IMRT and its dosimetric advantages might not guarantee a negligible risk of ORN. In a recent multi-institutional study of IMRT for early oropharyngeal cancer conducted by the Radiation Therapy Oncology Group (RTOG), an ORN rate of 6% (4 of 69 patients) was reported (30). In that study (RTOG 00-22), the prescribed high-risk PTV dose was 66 Gy in 30 fractions (2.2 Gy/fraction), and the mandibular maximal doses were limited to 72 Gy (33). No major dosimetric violation of the protocol dose constraints occurred in the cases that developed ORN; however, it is possible that the higher-than-standard fraction doses delivered to the part of the mandible adjacent to the PTVs may have played a role in the cases of ORN.

Another potential reason for the greater than expected incidence of ORN in RTOG 00-22 was the lack of standardized prophylactic dental care in that study. Guidelines for prophylactic dental care in this protocol were provided in a single sentence (“Any dental repairs must be made and prophylaxis instituted before therapy”) (31). Less-than-optimal prophylactic care was possible, especially in institutions treating small number of patients. This issue is reflected by the lack of any details of protocol dental care in publications that have summarized the results of recent important clinical trials in head-and-neck cancer (32–37). This omission has been corrected in the most recent RTOG head-and-neck cancer protocols, which have included appendices detailing the recommended dental care. These recommendations, if adhered to, are expected to reduce the rates of ORN in multi-institutional studies to the very low rates reported by institutions treating large numbers of head and neck cancer patients.

Controversy exists regarding some of the traditional dental care paradigms associated with the prevention of ORN. An extensive discussion of these controversies has recently been provided by Wahl (38). Extraction of healthy or restorable teeth before RT starts, practiced in previous years, is no longer recommended and was not practiced in our patients.

In contrast, extraction of decaying and nonrestorable teeth has been a cornerstone of our prophylactic dental care. The prevention of ORN by HBO in patients requiring post-RT teeth extraction is another contentious issue discussed at length by Wahl (1). Randomized studies of HBO vs. no HBO before post-RT teeth extractions showed significant benefits for the HBO arms; however, the rates of ORN in the control arms seem to be greater than in other, nonrandomized studies. In our series, 2 patients requiring post-RT teeth extractions from parts of the mandible that had received a high dose received HBO before extraction and 4 did not, and none developed ORN. Another common practice is the use of prophylactic antibiotics before post-RT teeth extractions, for which no firm evidence of efficacy has been found (1).

Apart from these controversies, the principles of pre-RT prophylaxis include extraction of decaying or nonrestorable teeth, strict dental care, including daily topical fluoride and the use of dental protective stents to reduce scattered radiation off metal teeth restorations into the neighboring soft tissue, have been the cornerstone of the dental preventive care practiced in this series. We found the latter device (detailed in the “Methods and Materials” section) to be effective in reducing acute mucositis in the soft tissue surrounding the restored teeth. The overdosage due to backscatter off the high-gold alloy was calculated to be 30% and 0 at 1 mm and 4 mm off the tooth, respectively (38). Therefore, a thickness of 4 mm is required for the stent to minimize the increased dose to the soft tissue near the tooth. Reducing such “hot spots” around restored teeth may have contributed to reduced mucosal damage causing bony exposure and consequent ORN. In addition, the use of daily topical sodium fluoride gel application by a custom-made fluoride carrier has markedly reduced the risk of caries (39), and it has been a routine practice in our institution. All patients received this device, and they were asked during follow-up visits whether they had continued to routinely use it. However, details regarding the long-term compliance were not available, notwithstanding the costs of the prescribed fluoride and lack of insurance coverage of these costs for many patients.

CONCLUSION

No cases of ORN were observed in this series of IMRT for head and neck cancer. The potential factors contributing to the lack of this complication included reduced mandibular volumes receiving high doses, improved salivary flow rates and associated improved oral health, and uniform prophylactic dental care. We do not know which factor was the most important. However, because of the reported occurrences of ORN in a multi-institutional study of IMRT in which a uniform dental care protocol was not applied, we suspect that the dental prophylactic care, as detailed in our report, was a major factor in reducing ORN risk. Meticulous dental care policies should be an integral part of the treatment of head and neck cancer.

REFERENCES


