Risk Factor Assessment for the Development of Osteoradionecrosis

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Purpose: Osteoradionecrosis (ORN) of the jaws has been extensively studied. However, controversy still exists regarding its etiology, risk factors, and the underlying mechanism of disease. The purpose of this study was to identify and evaluate significant risk factors for the development of ORN.

Patients and Methods: This was a retrospective cohort study of 82 Massachusetts General Hospital patients radiated for head and neck cancer between 1984 and 2005. Patient records were reviewed to collect demographic information, medical and dental history (including dental intervention or trauma), tumor specific data, treatment details, and follow-up. Biologic variables (ie, age and gender) of potential significance were also evaluated. The major outcome variable was the development of ORN or lack of development of ORN. The time from radiation to ORN, or for non-ORN patients, time to last follow-up visit, was computed. Univariate analyses identified candidate variables associated with ORN ($P < .15$). Cox proportional hazards regression was used to evaluate these candidate variables as well as biologically relevant variables. Significant prognostic factors for the development of ORN ($P < .05$) were identified.

Results: Multivariate regression identified the following variables as significantly associated with decreased ORN risk: higher body mass index ($P = .02$) and use of steroids ($P = .02$). Radiation dose greater than 66 Gray ($P = .03$) was associated with an increased ORN risk.

Conclusions: Optimization of nutritional status, use of steroids, and limitation of total radiation dose may minimize the risk of ORN.

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Osteoradionecrosis (ORN) of the jaws is a recognized complication of radiation therapy for malignant tumors of the head and neck. Despite extensive literature documenting research and clinical experience, the underlying mechanism of ORN remains controversial.1-8 Treatment protocols vary and include combinations of antibiotics, debridement, mandibulectomy, vascularized soft tissue and bone grafts, and hyperbaric oxygen (HBO) therapy. Frequently, patient outcomes are poor. A better understanding of risk factors for the development of ORN and of the underlying pathophysiology may improve our ability to prevent this complication and help to improve the prognosis for those being treated for ORN.

In 1970, Meyer outlined a theory of pathogenesis for ORN.9 He hypothesized that osteonecrosis resulted from radiation injury to the bone and soft tissue followed by trauma (eg, tooth extraction or ridge irritation) and secondary infection. The vascular compromise induced by radiation sensitized the bone to bacterial infiltration. He recommended operative debridement of necrotic bone and a course of antibiotics.

However, there was little pathologic evidence to support Meyer’s hypothesis. In the majority of ORN tissue specimens, there was an absence of bacterial...
In 1983 Marx proposed a new biologic model for ORN. He suggested that radiation produced a vascular injury causing the bone and overlying soft tissue to become hypovascular, hypocellular, and hypoxic (the so-called “three H hypothesis”). Depending upon the severity of unmet oxygen and nutritional demands, the damaged tissue could undergo spontaneous necrosis or necrosis induced by trauma. In traumatically induced cases, the affected tissue’s ability to heal was inadequate. Marx advocated for the use of prophylactic and therapeutic HBO therapy in an effort to stimulate monocyte and fibroblast growth and to increase the expression of vascular endothelial growth factor with secondary angiogenesis. After comparing antibiotic-treated versus HBO-treated patients undergoing dental extractions, he concluded that HBO therapy significantly lowered the risk of developing ORN. However, there are few studies duplicating Marx’s results. A recent randomized, controlled, double-blind trial reported no preventive benefit in the HBO treated group undergoing extractions. In this study, there was actually an increased risk of ORN in patients receiving prophylactic HBO.

In 2004, Assael hypothesized that ORN occurs by the same mechanism as other types of osteonecrosis (eg, bisphosphonate-related osteonecrosis) and results from decreased osteoclastic bone resorption. Increased subperiosteal bone deposition in ORN specimens and thickening of the jaw in radiated zones support this theory. Without osteoclasts to resorb the nonviable, radiated bone, healing is impaired. However, there is contradictory evidence to suggest that bisphosphonates may promote healing in patients with ORN. In a 2005 study, using DNA hybridization, investigators showed that bacteria may in fact play a fundamental role in the pathogenesis of ORN, supporting Meyer’s original hypothesis. A current theory proposes that ORN occurs by a radiation-induced fibroatrophic mechanism including free-radical formation, endothelial dysfunction, inflammation, microvascular thrombosis, fibrosis and remodeling, and finally bone and tissue necrosis.

In light of the unclear pathogenesis, a multitude of potential etiologic factors for this disease entity and poor outcomes of treatment, identification of those patients at greatest risk prior to developing ORN is critically important. Risk factors include variables related to patient demographics, health status, dental health, the radiation treatment itself, the tumor or a traumatic challenge. A review of the available literature implicates the following candidate variables for development of ORN: total radiation dose, photon energy, brachytherapy, field size, fractionation, periodontitis, preirradiation bone surgery, poor oral hygiene, alcohol and tobacco use, dental extractions, tumor size, location, and stage, proximity of tumor to bone, lack of HBO therapy, increased time since radiation, lack of radiation shields, and edentulousness.

Despite the extensive literature on the subject of ORN, evidence of consistent and conclusive risk exists for only a fraction of factors examined. Furthermore, many of the publications are case reports or case series with no disease-free controls and small sample sizes. In a few larger and well-designed studies, some risk factors have been identified. To date, the findings in these studies have not been replicated. In addition, very little information exists regarding the relationship between systemic disease and the development of ORN. Such comorbidities as osteoporosis, autoimmune diseases, nutritional compromise, and others may play a role in disease progression. Finally, the use of paclitaxel (a taxane) as a radiosensitizer has not been studied in relation to ORN risk. The purpose of this study is to identify and evaluate a comprehensive group of potential risk factors associated with the development of ORN. Many have been evaluated in previous studies. Others originate in newer theories of pathogenesis. We hypothesize that in a subset of radiated patients, such analysis will identify those variables significantly associated with ORN risk.

**Patients and Methods**

This retrospective cohort study involved 82 Massachusetts General Hospital patients. All subjects had a history of head and neck cancer and received radiation therapy during the period from 1984 through 2005. Patients were identified using the Partners Healthcare System, Inc Research Patient Data Query Tool. Additional inclusion criteria included availability of complete medical and radiation therapy (XRT) records. This cohort consisted of two subgroups: 1) ORN patients: 41 patients meeting the above inclusion criteria who were diagnosed with ORN during the follow-up period; and 2) non-ORN patients: 41 patients meeting the above inclusion criteria who did not develop ORN.

**CANDIDATE VARIABLES**

We recorded over 50 variables for each patient and grouped them into the following categories: 1) Patient related: age, tobacco, alcohol, exercise, body mass index (BMI), use of statin drugs, steroid use, use of antifolate medication, use of sickle-cell medication, pro- and anti-coagulant use; 2) health Status: Diabetes, collagen-vascular disease, hypertension, thyroid disease, arthritis, renal disease, liver disease, HIV, anemia, thromboembolism history, human
papilloma virus, hyperlipidemia, hypoalbuminemia, osteopenia/osteoporosis; 3) dental: oral hygiene, periodontitis, endodontic status, caries, dentures; 4) tumor related: tumor stage, site, histology, and involvement of bone; 5) treatment related: total radiation dose, field size, electron versus proton, fractionation, brachytherapy, shielding, time after XRT that ORN developed, antibiotics, HBO therapy, adjunctive chemotherapy treatment, use of radioprotective agents, use of radiosensitizers; and 6) trauma related: time after XRT trauma occurred, extractions, number of teeth extracted, other surgery or trauma (eg, implants), smoothing of sharp alveolar ridges, location of extracted teeth, surgical versus simple extraction. (“Trauma” included tooth extractions, alveoloplasty, dental restorations, implants, bridge placement, endodontic therapy, biopsy, and distraction osteogenesis.)

OUTCOME VARIABLES

The outcome variables of interest were development of ORN or lack of development of ORN. Follow-up time was calculated as the time between date of radiation therapy and development of ORN, or the date of the last follow-up visit for patients who did not develop ORN.

DATA MANAGEMENT AND ANALYSIS

Descriptive statistics were computed. Univariate analysis identified variables (prognostic factors or covariates) associated with ORN. Multiple multivariate regression models to identify significant prognostic factors ($P < .05$) were used to analyze variables with $P$ less than .15 on univariate analysis and biologically relevant variables. Estimates of the regression coefficients and their standard errors with 95% confidence interval were calculated. We used Cox proportional hazards regression model because the outcome variable (time to ORN) involved follow-up time. The final multivariate regression model identified independent predictors of an adverse outcome (ORN). All statistical analyses were performed using the SAS version 8.2 software (2001; SAS Institute, Cary, NC).

Results

DEMOGRAPHICS

The cohort was 72% male and average age at radiation was 61 years (range 36-82). Ninety-five percent had external beam radiotherapy and 5% had brachytherapy. Follow-up time averaged 47.83 months ± 49.66 (range, 0-242 months). Mean time to development of ORN was 52.53 months ± 54.73 and mean follow-up time of those who did not develop ORN was 43.24 months ± 44.36.

UNIVARIATE ANALYSIS

On univariate analysis (Table 1), 10 factors associated with ORN risk ($P < .15$) were identified. Those associated with a higher risk included radiation dose greater than 66 Gray (Gy) and a history of trauma before or after XRT. Those factors associated with a decreased risk included pack-years smoking, higher BMI, elevated glucose level, hypertension, anticoagulant use (aspirin, heparin, warfarin), statin use, steroid use (inhaled or systemic), gastroesophageal reflux disease, and osteoporosis.

MUTIVARIATE ANALYSIS

Our final multivariate model consisted of five candidate variables from the univariate results (Table 2), including radiation doses greater than 66 Gy, trauma after radiation, BMI, anticoagulant use, and steroid use. We also studied demographic and biologically relevant variables. Estimates of the regression coefficients and their standard errors with 95% confidence interval were calculated. We used Cox proportional hazards regression model because the outcome variable (time to ORN) involved follow-up time. The final multivariate regression model identified independent predictors of an adverse outcome (ORN). All statistical analyses were performed using the SAS version 8.2 software (2001; SAS Institute, Cary, NC).

Table 1. UNIVARIATE ANALYSIS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation, &gt;66 Gy</td>
<td>2.708*</td>
<td>1.061-6.915</td>
<td>.0373</td>
</tr>
<tr>
<td>Trauma post-XRT</td>
<td>2.318*</td>
<td>1.197-4.491</td>
<td>.0127</td>
</tr>
<tr>
<td>Trauma (yes)</td>
<td>2.239*</td>
<td>1.144-4.383</td>
<td>.0186</td>
</tr>
<tr>
<td>Pack years</td>
<td>0.982†</td>
<td>0.969-0.995</td>
<td>.0076</td>
</tr>
<tr>
<td>Higher BMI</td>
<td>0.897†</td>
<td>0.822-0.978</td>
<td>.0142</td>
</tr>
<tr>
<td>Higher glucose</td>
<td>0.614†</td>
<td>0.320-1.180</td>
<td>.1434</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.603†</td>
<td>0.314-1.155</td>
<td>.1270</td>
</tr>
<tr>
<td>Use of anticoagulants</td>
<td>0.463†</td>
<td>0.213-1.006</td>
<td>.0518</td>
</tr>
<tr>
<td>Use of statins</td>
<td>0.370†</td>
<td>0.110-1.243</td>
<td>.1079</td>
</tr>
<tr>
<td>Use of steroids</td>
<td>0.353†</td>
<td>0.140-0.890</td>
<td>.0273</td>
</tr>
<tr>
<td>GERD</td>
<td>0.306†</td>
<td>0.085-1.099</td>
<td>.0695</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0.158†</td>
<td>0.037-0.682</td>
<td>.0134</td>
</tr>
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</table>

Abbreviations: BMI, body mass index; GERD, gastroesophageal reflux disease; XRT, radiation therapy.

*Associated with higher risk.
†Associated with decreased risk.


Table 2. MULTIVARIATE ANALYSIS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.73</td>
<td>0.56-0.950</td>
<td>.019*</td>
</tr>
<tr>
<td>Use of steroids</td>
<td>0.04</td>
<td>0.003-0.560</td>
<td>.017*</td>
</tr>
<tr>
<td>XRT &gt;66 Gy</td>
<td>10.95</td>
<td>1.32-0.9086</td>
<td>.027*</td>
</tr>
<tr>
<td>Age at XRT</td>
<td>1.04</td>
<td>0.97-1.110</td>
<td>.258</td>
</tr>
<tr>
<td>Gender</td>
<td>0.19</td>
<td>0.02-1.520</td>
<td>.118</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>0.31</td>
<td>0.06-1.710</td>
<td>.181</td>
</tr>
<tr>
<td>Trauma after XRT</td>
<td>2.41</td>
<td>0.43-13.42</td>
<td>.317</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; XRT, radiation therapy.

*Statistically significant variables ($P < .05$).

increased by 27% (relative risk for every one point increase in BMI, ORN risk decreased by 4.50 (range, 1.62-32.66). On multivariate analysis, while the BMI of those who did not averaged 25.13, ORN averaged 23.02. The BMI of patients who did not receive radiation doses greater than 66 Gy. Age at radiation, gender of the patient, anticoagulant use and trauma after radiation did not significantly alter ORN risk.

**Discussion**

In this study, the BMI of patients who developed ORN averaged 23.02 ± 4.05 (range, 15.65-29.61) while the BMI of those who did not averaged 25.13 ± 4.50 (range, 16.28-32.66). On multivariate analysis, for every one point increase in BMI, ORN risk decreased by 27% (relative risk = 0.73). The 2-point difference between the average BMI of 25 in non-ORN patients and a BMI of 23 in ORN patients is not only statistically significant, but also clinically relevant because 1 group was overweight while the other was not. This association between increased BMI and lower incidence of ORN is important because the effects of surgery, radiation, and chemotherapy often compromise the nutritional status of these patients.

We further stratified the patients to see if and when increasing BMI no longer protects against ORN. Using the underweight group (BMI < 18.5) as our reference of highest ORN risk, we compared the risk to normal weight (BMI 18.5-24.9), overweight (BMI 25-29.9), and obese (BMI ≥ 30) patients. Compared with underweight patients, risk of ORN decreased by 50% in those with normal BMI, by 43% in overweight individuals, and by 37% in obese patients. However, the decrease in ORN rate was only statistically significant in the overweight group (P = .03). Mildly overweight patients may have had less severe disease, eg, smaller tumors and a lower incidence of metastatic disease and hence maintained their appetite and ability to eat during treatment. Though obese patients also exhibit sustained appetite and adequate nutrition, the additional comorbidities associated with obesity may increase the risk of ORN compared with mildly overweight patients. Our study suggests that a higher BMI at any level protects against ORN, but not significantly so in the obese range.

Though repeatedly implicated as increasing ORN risk, in this study, trauma after radiation therapy was not associated with a significant increased risk on multivariate analysis. When adjusting for age, gender, anticoagulant use, BMI, steroid use, and radiation doses greater than 66 Gy, the increased risk associated with trauma, though almost 2.5 times as great, did not reach statistical significance. It is possible that the lack of association of trauma and increased ORN risk in this study was an artifact of small sample size, or the benefit of increased BMI on wound healing.

Another important finding was that 54% of non-ORN patients compared with 28% of the ORN patients took steroids before or after radiation therapy. On multivariate analysis, steroid use before or after radiation reduced the risk of ORN by 96% (relative risk = 0.04). These results support the "radiation-induced fibrosis" theory which occurs in 3 stages: 1) radiation damage of endothelial cells induces cytokine release, causing increased vascular permeability and exposure of subendothelium to blood products; inflammation and microvascular thrombosis ensue; 2) fibroblast activation, via interaction with reactive oxygen species created by radiation, leads to fibrosis and atrophy; and 3) necrosis. The protective effect of steroids is not surprising based on this hypothesis. Their anti-inflammatory effects may inhibit the initial inflammatory phase of ORN, thereby preventing progression to thrombosis, atrophy, and necrosis. The finding that anticoagulants are significantly reduced ORN risk on univariate analysis also lends credibility to the radiation-induced fibrosis hypothesis. Prevention of thrombosis may be important in preserving the microvascular blood supply to radiated tissues. It should be noted that we included aspirin under the category of "anticoagulant," so the benefit may result primarily from the anticoagulation effects, the anti-inflammatory effects, or both. The use of aspirin in radiated patients merits further exploration because of its wide availability, affordability, and low side effect profile compared with steroids. Finally, we recorded steroid usage as a binary event, with a positive data point if the patient used inhaled or systemic steroids any time after cancer diagnosis until the last follow-up visit or development of ORN. The association of decreased incidence of ORN in patients who took steroids was noted upon data analysis when it was found to be a significant variable. In future studies, therefore, steroid usage, eg, dose, route, duration and relationship to radiation therapy warrants investigation.

Though radiation dose undoubtedly contributes to the development of ORN, no consensus exists in the literature as to maximal safe dosing. Conclusions range from 50 to 90 Gy. In this study, the mean radiation dose for patients who developed ORN was 67.69 Gy ± 8.75 (median, 70 Gy; range, 40-80 Gy). The mean radiation dose for controls was 68.7 Gy ± 12.48 (median, 69.8 Gy; range, 44-130 Gy). Though the difference in means is insignificant, 73% of patients who developed ORN received radiation doses greater than 66 Gy compared with only 56% of
those who did not develop ORN. Receiving a radiation dose above 66 Gy increased risk of developing ORN by almost 11-fold. This finding confirms the results of studies reporting the harmful effect of doses over 65 Gy. However, because some ORN patients received doses significantly lower than 66 Gy and most non-ORN patients received doses of 66 Gy or higher, it seems clear that dose by itself does not predict absolute risk.

Noteworthy variables that showed no increased ORN risk included increased age at the time of radiation, male gender, smoking and alcohol use, tumor stage, and chemotherapy. These factors have previously been reported to increase ORN risk. Diabetes, kidney and liver dysfunction, and anemia also did not correlate with increased ORN risk. Hypoalbuminemia also did not confer an increased ORN risk, despite our finding of increased risk for patients with a lower BMI. Of interest, HBO therapy did not decrease ORN risk in this cohort. Bisphosphonate use did not affect (positively or negatively) risk of developing ORN. The use of a radiosensitizer (ie, paclitaxel) during treatment did not increase the risk of ORN. Of the 4 patients in the cohort who received brachytherapy, 2 developed ORN. However, the limited number of patients treated with this mode of radiation did not permit a determination of statistical significance.

The retrospective nature of the data collection was a limitation of this study. Missing data points and varying recording methods made it challenging to find a consistent way to evaluate certain risk factors. Most medical charts did not contain detailed information regarding the patient’s dental status. The follow-up period for the patients without ORN was 10 months shorter than the ORN group. It is possible, therefore, that given more time, some of the controls might have eventually developed ORN. Due to time and resource restrictions, we studied a limited number of patients. With a power of 70%, our findings are suggestive though not definitive, and should continue to be studied in a larger sample.

Finally, in this study a subset of patients radiated for head and neck cancer during a given time period were evaluated, but we did not look at the complete cohort of patients that met these criteria. Therefore, while most closely resembling a retrospective cohort study, we could not calculate a true incidence of ORN in this population. We intentionally selected 41 patients who developed ORN and 41 who did not, but we do not assume an ORN incidence of 50% in radiated patients.

Despite its limitations, the results of this study indicate that optimization of nutritional status, use of steroids in the peritreatment period, and limitation of total radiation dose may minimize the risk of ORN.

Further study, with a larger sample size is indicated to confirm these findings.

References