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Predicting radiation dosimetric distribution in different regions of the jaw in patients receiving radiotherapy for squamous cell carcinoma of the tonsil

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Abstract

Background: Radiotherapy (RT), the main treatment for patients with head and neck cancer, can lead to dental complications.

Methods: We identified 244 patients with squamous cell carcinoma of the tonsil treated with RT from 2004 to 2013. For each patient, we contoured the 10 tooth-bearing regions and calculated the radiation dose (gray, Gy) to each region. From this data set, we built two predictive models to determine the expected maximum radiation dose, one for the non-molar regions and another for the molar regions.

Results: For the non-molars, the final model included location, T-classification, and overall stage, with a median absolute prediction error of 7.0 Gy. For the molars, the final model included location, T-classification, overall stage, and treatment year, with a median absolute error of 6.0 Gy.

Conclusions: Our current model offers a good estimation of the maximum radiation dose delivered to different regions of the jaw; future work will independently validate these models.

KEYWORDS
dental complications, dose modeling, head and neck cancer, radiation, radiotherapy

1 | INTRODUCTION

Squamous cell carcinomas of the head and neck are primarily treated with radiotherapy (RT).[1] The proximity of normal structures such as the jaws, salivary glands, and mandibular and maxillary bones to primary tumor sites often results in increased radiation exposure to these regions. Although the development of intensity-modulated radiotherapy (IMRT) has improved the ability to deliver radiation conformal to tumor sites, there is still inevitable radiation exposure to surrounding healthy organs and tissues.[2-4]

Chiaojung Jillian Tsai and Nipun Verma are co-first authors.

Acute oral toxicities following radiation to the head and neck include mucositis and hyposalivation. Late toxicities include osteoradionecrosis (ORN) to the mandible and maxilla, as well as subsequent dental complications (eg, dental caries and periodontal disease). Hyposalivation, a prevalent complication, occurs following radiation induced damage to the salivary glands and results in a reduction of salivary flow, which can lead to difficulties with speech and swallowing. The development of sequelae such as dental caries, periodontal disease, and ORN is due to both a direct effect of radiation on tooth structure as well as hyposalivation, which reduces oral clearance and alters oral microflora.[5] Additionally, radiation-induced fibrosis of bone, chronic inflammation, concurrent chemotherapy, and physical trauma from surgery can exacerbate the development of ORN.[6]

Numerous studies have correlated the radiation dose delivered with the development of adverse sequelae.[7-10] In our own institution, multivariate analysis of over 1000 patients found that higher radiation dose was a significant risk factor for the development of ORN.[11] This has led to recommendations of the maximum dose that structures such as the parotid gland, mandible, and teeth can safely be

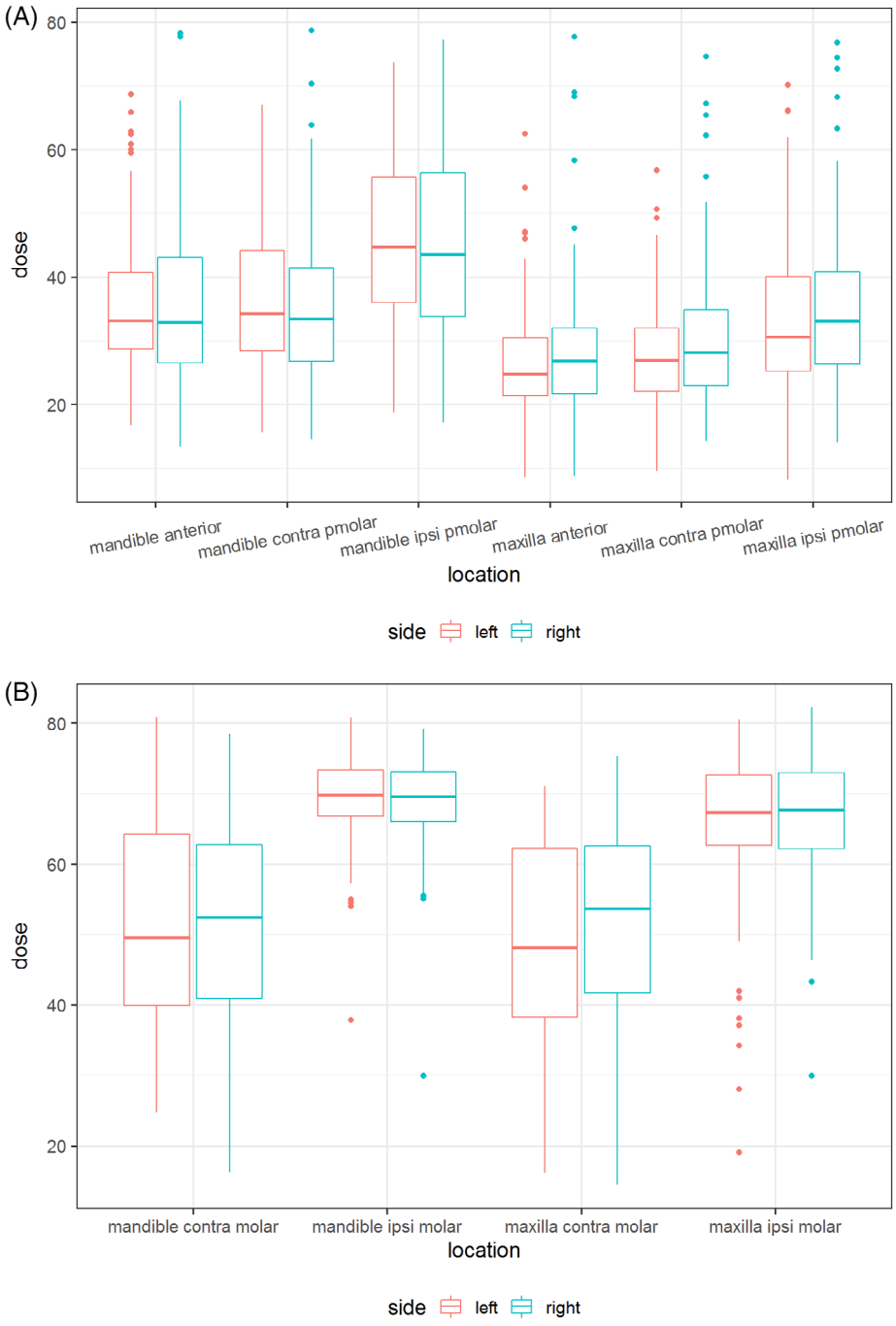

FIGURE 1 Measured maximum radiation dose delivered to six non-molar (A) and four molar (B) regions. Premolars (pmolar) and dental regions ipsilateral (ipsi) and contralateral (contra) to the primary tumor are indicated [Color figure can be viewed at wileyonlinelibrary.com]

exposed to.[12-14] However, information regarding radiation dose to specific regions of the maxilla and mandible or tooth-bearing regions is often not readily available to dental practitioners. Accurate assessment of radiation dosage to dental structures is essential for post-RT dental management. This includes an evaluation of the risk of dental complications, which, in turn, influences the aggressiveness of monitoring for toxicities and the necessity of dental surgical intervention, such as tooth extraction.

Here, we present two prediction models that can be used to estimate the maximum radiation dose delivered to different regions of the oral cavity following RT. These models were determined from 244 patients with squamous cell carcinoma of the tonsil treated with IMRT at Memorial Sloan Kettering Cancer Center (MSKCC) from 2004 to 2013.

2 | PATIENTS AND METHODS

2.1 | Patient population

This retrospective study was approved by MSKCC Institutional Review Board, and written informed consent was obtained to review patient records. We reviewed records of 244 patients with tonsil cancer treated with IMRT in our institution between 2004 and 2013. The following clinical information was available to us: demographic data, tumor site, tumor diagnosis, tumor category, radiation prescription dose to the primary tumor, dental events, social history (alcohol and smoking history), and medical comorbidities.

2.2 | Patient treatment

Patient treatment was delivered with a seven to nine posterior IMRT beams using 6 MV photons. In some cases, a low anterior neck field was also used and matched to the upper neck fields. A single integrated boost approach was used to deliver 70 Gy to the planning target volume based on the gross tumor volume; 59.4 Gy to high-risk subclinical disease; and 54 Gy to low-risk subclinical disease. All patients received concurrent chemotherapy. A more detailed description of these treatments can be found in Setton et al.[15]

2.3 | Definition of dental regions and contouring

The tooth-bearing regions of the maxilla and mandible/jaws were divided into 10 dental regions. For each patient, the mandible in its entire height, from the alveolar crest to the inferior cortex, was manually contoured for the bone surrounding the right molars, left molars, right premolars, left premolars, and anterior teeth (canine to canine). Cumulative dose-volume histograms were produced for each mandibular region in each patient, and the average of the mean and the maximum point doses for each defined region were calculated. Further analysis and construction of the predictive models were based on the calculated maximum point doses. Regions were evaluated based on ipsilaterality or contralaterality to the primary tumor site. For more detailed information, please refer to Hansen et al.[16]

2.4 | Statistical analysis

In order to model the dose received to each region of the jaws, multivariate generalized estimating equation models were fit using an exchangeable correlation structure to account for the correlation among regions within the same individual's mouth. Candidate predictors of interest included tumor side (left, right), overall stage (I-III, IV), T-classification (1-2, 3-4), N-classification (0/1, 2a/2b, 2c/3), and treatment year (2004-2013). Due to skewness in the dose received, separate models were constructed for the molar regions

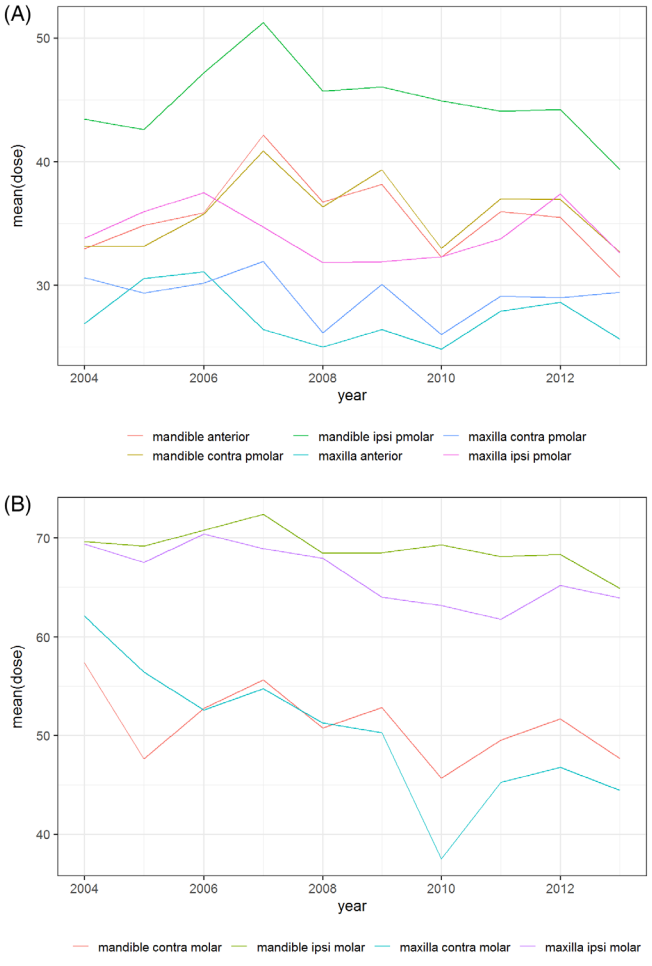

FIGURE 2 Average of the measured maximum radiation dose for six non-molar (A) and four molar (B) regions for each radiation year (2004-2013). Premolars (pmolar) and dental regions ipsilateral (ipsi) and contralateral (contra) to the primary tumor are indicated [Color figure can be viewed at wileyonlinelibrary.com]

(mandible/maxilla contralateral/ipsilateral molars) and non-molar regions (mandible/maxilla contralateral/ipsilateral premolars and mandible/maxilla anterior). For the non-molar regions, a log transformation was used to reduce skewness, whereas for the molar regions, a reflection around 100 Gy (an upper limit of observed dose) followed by a log transformation was employed to reduce skewness.

3 | RESULTS

The measured maximum radiation doses for the six regions of non-molar teeth (a) and four regions of molar teeth (b) in the 244 patients are shown in Figure 1. Overall, molar teeth had greater radiation exposure than non-molar teeth and dental regions ipsilateral to the tumor had greater radiation exposure than the corresponding contralateral region. For the premolar categories specifically, regions within the mandible had greater radiation exposure than regions within the maxilla. The measured maximum radiation dose delivered to different non-molar (Figure 2A) and molar regions (Figure 2B) was also compared with the year of radiation treatment. For non-molar regions and ipsilateral molar regions, the radiation dose was relatively unchanged from 2004 to 2013; however, contralateral molars in the mandible and maxilla showed a decline in radiation dose in 2013 compared to 2004.

From this data set, we built two predictive models to determine the expected maximum radiation dose, one for the six non-molar regions and another for the four molar regions. For the non-molars, the final model included location, T-

TABLE 1 Values for variables (location, T-category, overall stage, year) used for non-molar and molar predictive models

	Variable	Estimate (95% CI)	*P*-value
Non-molar	Intercept	3.399 (3.332, 3.466)	<.001
	Location		<.001
	Mandible anterior	reference	
	Mandible contra premolar	0.001 (−0.030, 0.033)	
	Mandible ipsi premolar	0.234 (0.206, 0.262)	
	Maxilla anterior	−0.275 (−0.320, −0.230)	
	Maxilla contra premolar	−0.207 (−0.250, −0.164)	
	Maxilla ipsi premolar	−0.055 (−0.100, −0.010)	
	T-category		<.001
	1-2	reference	
	3-4	0.163 (0.097, 0.229)	
	Stage		.002
	I-III	reference	
	IV	0.105 (0.038, 0.173)	
Molar	Intercept	−43.113 (−58.400, −27.826)	<.001
	Location		<.001
	Mandible contra molar	reference	
	Mandible ipsi molar	−0.432 (−0.467, −0.397)	
	Maxilla contra molar	0.024 (−0.007, 0.055)	
	Maxilla ipsi molar	−0.362 (−0.404, −0.319)	
	Year	0.023 (0.016, 0.031)	<.001
	T-category		<.001
	1-2	reference	
	3-4	−0.119 (−0.163, −0.076)	
	Stage		<.001
	I-III	reference	
	IV	−0.100 (−0.149, −0.050)	

Dental regions ipsilateral (ipsi) and contralateral (contra) to the primary tumor are indicated.

Abbreviations: CI, confidence interval; contra, contralateral; ipsi, ipsilateral.

classification, and overall stage (American Joint Committee on Cancer [AJCC] 7th edition). The values used for each of these variables are shown in Table 1. Not surprisingly, patients with overall stage IV or T3-4 disease had a significantly greater dose received than patients with overall stage I-III or T1-2 disease. The largest expected doses were exhibited in the mandible ipsilateral premolars, followed by the mandible contralateral premolars, mandible anterior, maxilla ipsilateral premolars, maxilla contralateral premolars, and maxilla anterior. The median and range of calculated maximum doses for non-molar regions using the predictive model are shown in Table 2. The median (range) absolute prediction error across all non-molar regions was 7.0 Gy (0-48 Gy). A scatterplot of calculated vs measured doses and the absolute prediction errors for each non-molar region are shown in Figure 3A.

For the molars, the final model included location, T-classification, stage, and treatment year. The values for each of these variables are shown in Table 1. Similar to the non-molar regions, patients with overall stage IV or T3-4 had a greater expected dose received than patients with overall stage I-III or T1-2, and patients treated more recently exhibited a decrease in the maximum dose received. The largest expected doses were exhibited in the mandible ipsilateral molars, followed by the maxilla ipsilateral molars, mandible contralateral molars, and maxilla contralateral molars. The median and range of calculated maximum doses for molar regions using the predictive model are shown in Table 2. The median (range) absolute prediction error across all molar regions was 6.0 Gy (0-42.2 Gy). A scatterplot of calculated vs measured doses and the absolute prediction errors for each molar region are shown in Figure 3B. Nomograms for non-molar (a) and molar regions (b) are shown in Figure 4.

TABLE 2 The median and range of calculated maximum radiation doses for non-molar regions and molar regions using the predictive models

	Location	Median	Range
Non-molar	Overall	31.8	22.7-49.5
	Mandible anterior	33.3	29.9-39.2
	Mandible contra premolar	33.3	30.0-39.2
	Mandible ipsi premolar	42.1	37.8-49.5
	Maxilla anterior	25.3	22.7-29.7
	Maxilla contra premolar	27.0	24.3-31.8
	Maxilla ipsi premolar	31.5	28.3-37.1
Molar	Overall	61.2	40.3-75.4
	Mandible contra molar	53.1	41.7-62.1
	Mandible ipsi molar	69.5	62.1-75.4
	Maxilla contra molar	51.9	40.3-61.2
	Maxilla ipsi molar	67.3	59.4-73.6

Dental regions ipsilateral (ipsi) and contralateral (contra) to the primary tumor are indicated.

Abbreviations: contra: contralateral, ipsi: ipsilateral.

4 | DISCUSSION

The radiation dose to the tooth-bearing regions of the jaws is critically important in predicting dental and oral complications. Previous studies have retrospectively determined the radiation dosimetric distribution by contouring individual tooth-bearing regions in radiation treatment plans.[5,16-20] To our knowledge, this is the first article to generate models that could be used to predict expected radiation dose without requiring additional contouring. Reassuringly, the expected radiation doses from our predictive models followed similar trends as these studies that delineated individual teeth in the radiation treatment plans for base of tongue (BOT), tonsil, and hypopharyngeal tumors. These trends include a higher radiation dose for posterior teeth (molars followed by premolars) than for anterior teeth and greater radiation exposure of dental groups ipsilateral to the tumor than of dental groups contralateral to the tumor.[5,16,17,19,20] Tumor size was also found to be a predictive factor in our models for greater expected radiation dose, just as previous studies have found that larger tumors have greater radiation doses delivered to the anterior teeth and to the entire mandible (regardless of tumor laterality).[16,20] In our models, overall stage was a predictive variable for maximum radiation dose. Although an earlier study had not found a relationship between cervical nodal metastasis and mandibular radiation dose, it is possible that this conclusion was due in part to the small size of the sample group.[16]

The utility of our predictive models for clinical practice is dependent on whether they can as reliably predict subsequent oral complications as traditional methods of radiation dose measurement. A previous study contoured individual teeth to obtain a measured radiation dose, which was then correlated with tooth damage clinically determined by a dentist examiner using a previously validated index. Notably, radiation above a critical threshold of 60 Gy was associated with 10-fold greater risk of moderate to severe tooth damage.[10] Molar regions, based on both the measured and calculated maximum radiation doses, are more likely than non-molar regions to be exposed to doses greater than 60 Gy. Whereas the overall median absolute error was 6.0 Gy, when focusing only on those molar teeth with a measured maximum radiation dose greater than 60 Gy, the median absolute error decreased to 4.8 Gy.

The predictive models were generated from patients with squamous cell carcinoma of the tonsil. Previous studies have found that the distribution of radiation to tooth-bearing areas is dependent on the tumor site and its proximity to these dental regions. For BOT, tonsil, and hypopharyngeal tumors,

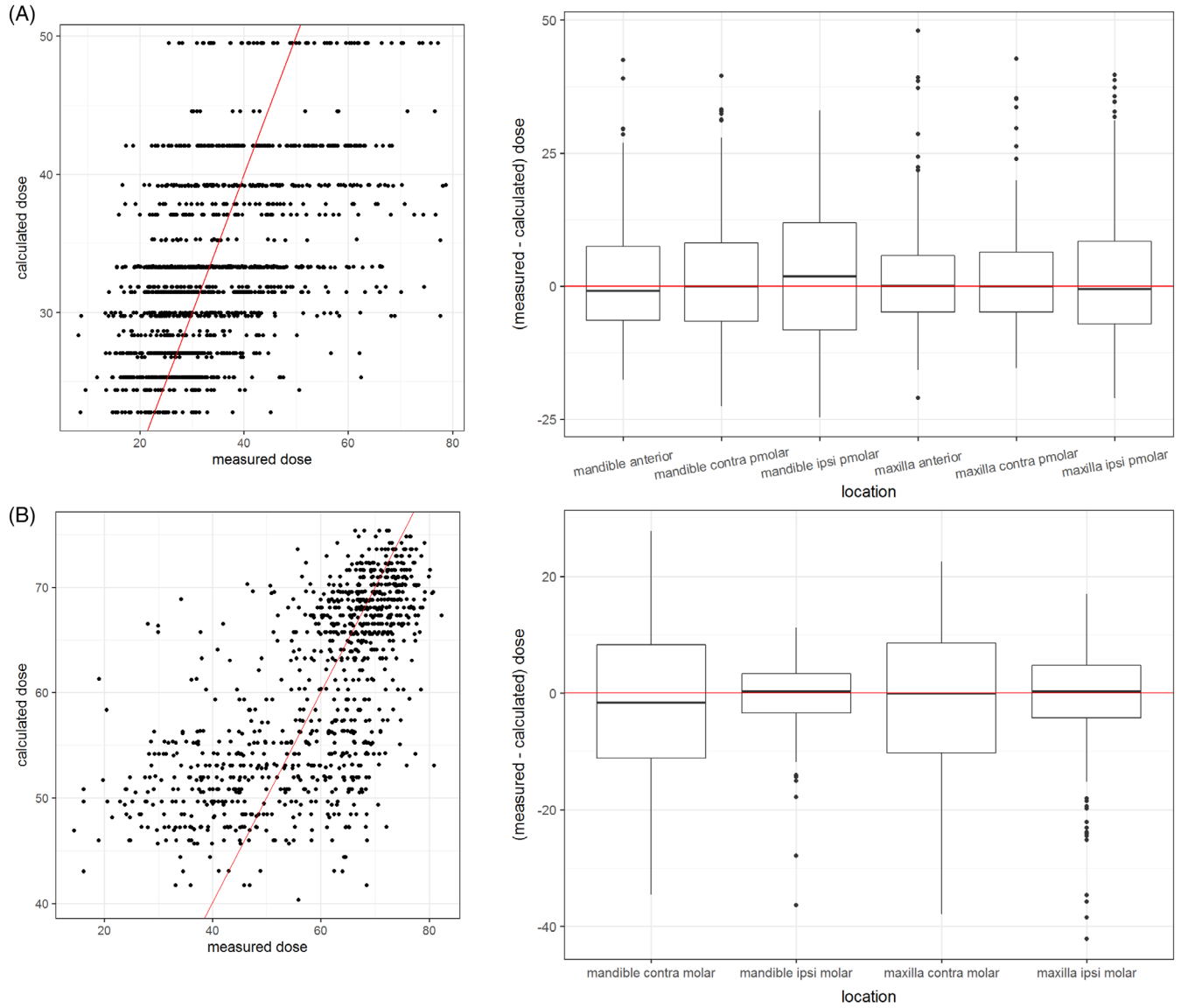

FIGURE 3 Scatter plots (calculated dose vs measured dose) and prediction error (measured − calculated) for maximum radiation dose for six non-molar (A) and four molar (B) regions. Premolars (pmolar) and dental regions ipsilateral (ipsi) and contralateral (contra) to the primary tumor are indicated [Color figure can be viewed at wileyonlinelibrary.com]

the posterior mandible received the greatest radiation doses, whereas the posterior maxilla had the greatest radiation exposure for nasopharyngeal cancers. In addition, different types of IMRT and even variation between radiation protocols of individual treatment centers may affect the radiation dosages delivered. Thus, our model will need to be validated and possibly adapted for these different disease and treatment groups. In the future, larger study populations can be used to generate predictive models that can be applied to diverse head and neck cancers (HNCs) and take into account variability in radiation oncology treatment procedures.

The longer survival times of patients with HNC requires the development of strategies to sustain quality of life following treatment. Although the radiation dosimetric distribution is necessary to evaluate risk for dental complications, the contouring of each individual tooth during radiation treatment planning is impractical. Instead, predictive models can be used to estimate radiation exposure to normal dental regions. These estimates could be used during treatment planning to identify patients particularly vulnerable to dental complications due to factors such as T-classification and overall stage. Identification of such patients could prompt further investigation of treatment plans to ensure radiation exposure of dental regions is minimized as much as possible. These models can also be combined with additional factors such as concurrent chemotherapy and surgical treatments, radiation exposure of salivary glands, and current dental and periodontal status to predict the risk of subsequent dental toxicities, and thus guide management decisions

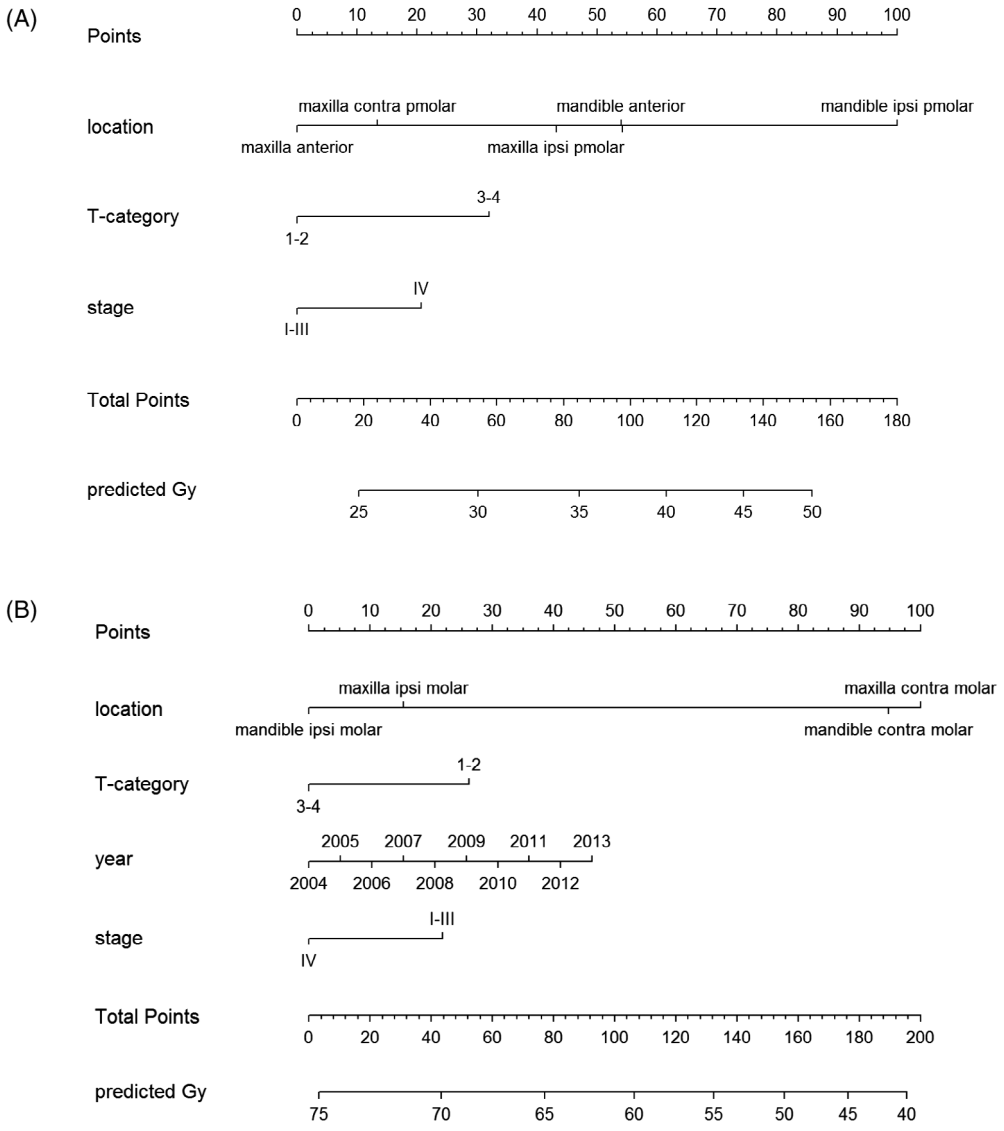

FIGURE 4 Nomograms for non-molar (A) and molar (B) regions. Premolars (pmolar) and dental regions ipsilateral (ipsi) and contralateral (contra) to the primary tumor are indicated

before and after RT. This would ensure that the benefits and risks of particular treatment plans, post-radiation monitoring, and treatment of associated toxicities are optimized.

This study develops the first predictive models to estimate radiation exposure to the jaws following RT for HNC. These predictive models estimated the radiation dose within an acceptable margin of error when compared to the direct measurement of radiation dose by contouring of individual teeth. The primary weakness of this study is that the predictive models were developed and tested on a data set of squamous cell carcinoma of the tonsils with a specific set of characteristics, which may limit the accuracy of these models for cases that differ from this data set. For instance, the predictive models are based on cases from a 9-year period (2004-2013) and are only applicable to those years as RT techniques and planning have improved since then leading to reduced dose distribution outside target volumes. The non-molar model cannot be used to predict doses greater than 100 Gy, due to the transformation applied to generate the model; however, 100 Gy is outside the range of doses used clinically, and doses in this range should not realistically be seen. Both predictive models are based on MSKCC planning techniques, which may differ from those used by other centers. Our models are not applicable to surgical patients in the adjuvant RT setting and are based on AJCC seventh edition staging. Finally, all cases within the data set were treated to 70Gy/59.4Gy/54Gy doses, which was the standard of care during the study period, but the recommended doses to elective regions may change over time. The radiation prescription also did not take into account human papillomavirus (HPV) status. Thus, these models are not applicable for patients who undergo deescalated therapy due to positive HPV. Nevertheless, by providing an estimation of maximum radiation dose, our predictive models are a valuable tool for dental practitioners to use when managing patients with HNC after

RT. Similar methodologies can be used to generate models for different disease subsites and account for recent treatment changes in the HPV era.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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