



ORIGINAL ARTICLE

# Radiation caries in nasopharyngeal carcinoma patients after intensity-modulated radiation therapy: A cross-sectional study



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## KEYWORDS

nasopharyngeal carcinoma;  
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tooth loss

**Abstract** *Background/purpose:* The exact dose of intensity-modulated radiation therapy (IMRT) associated with tooth damage is mostly unknown. We aim to evaluate the severity of dental lesions after IMRT and the correlation with the radiation dose to the dentition in patients with nasopharyngeal carcinoma (NPC).

*Materials and methods:* This was a cross-sectional study of 42 patients with NPC who completed IMRT in 2011. Each premolar tooth was divided into 13 sites. Teeth were evaluated using a validated index and subsequently categorized at each divided site. The relationship between dose distribution and the caries severity score was analyzed using logistic models. The odds of developing caries damage were evaluated using odds ratios.

*Results:* A total of 4342 sites from 334 premolar teeth were evaluated. For sites exposed to 30–60 Gy, the odds of developing caries damage were 12–200 times greater compared with sites

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unexposed to IMRT. A new radiation caries lesion was likely to occur when the dose was >35.8 Gy after 17 days' radiation therapy ( $P < 0.05$ ).

**Conclusion:** The findings suggest that new tooth damage was likely to occur at doses > 35.8 Gy, and care should be taken throughout the treatment planning process to limit tooth doses to < 50 Gy in NPC patients.

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## Introduction

Head and neck cancers are diagnosed in more than 500,000 people each year in the world.<sup>1</sup> Radiation therapy (RT) is indicated for nasopharyngeal carcinoma (NPC) and is particularly effective in type III NPC.<sup>2</sup> However, RT in the head and neck region will affect oral function and has important influences on quality of life.<sup>3</sup> Indeed, among other complications, irradiation of the head and neck area is accompanied by the development of radiation caries, which is a major cause of tooth loss and decreased quality of life.<sup>4</sup>

Clinically, rapid deterioration of the dental hard tissue is often observed.<sup>5</sup> Previous studies investigated the effects of RT on the organic matrix and mechanical properties of the human teeth *in vitro*<sup>6–9</sup> and *in vivo*,<sup>10,11</sup> and have suggested that radiation caries could be caused by the alteration of the dental hard tissues and/or hyposalivation. Irradiation of the enamel and dentine of the teeth can influence their mechanical structure by decreasing their ultimate tensile strength<sup>12</sup> and decreasing their fracture resistance. In dental research, radiation exposure to the major salivary glands causes a change in the composition of saliva qualitatively and a permanent quantitative reduction in secretion; this process contributes to the carious process.<sup>13</sup> Indeed, radiation-induced hyposalivation is considered to be the most important aetiological factor for dental caries.<sup>14</sup> However, some scientists have suggested that direct radiation damage can ratchet up the progression of radiation caries—in their studies, morphological and physical changes in both human and bovine dentine were documented after radiotherapy.<sup>6,15</sup>

After the completion of RT, patient quality of life may be drastically diminished as a result of numerous RT-induced oral complications including hyposalivation and severe breakdown of the dentition.<sup>5,16</sup> In the past, full-mouth tooth extraction was prescribed prior to RT; however, because removable prostheses were not often well-tolerated by the irradiated oral mucosa, the current approach is to maintain as many healthy teeth as possible.<sup>17</sup>

Nevertheless, previous studies have devised some approaches that could help decrease the frequency of tooth-related toxicities, with more or less success.<sup>5,16</sup> Intensity-modulated RT (IMRT) is a recent RT approach that is associated with improved survival and reduced toxicity in patients with NPC, compared with conventional two-field RT.<sup>18</sup> However, the relationship between radiation dose and the severity of radiation caries at different tooth sites still remain unclear.

Therefore, the aim of the present study was to evaluate the severity of dental lesions after IMRT and the association

with the radiation dose to the dentition in patients with NPC. Results of the present study could help design better RT approaches to limit radiation exposure of the teeth, and to identify the teeth that would need further prevention and care.

## Materials and methods

### Study design

This was a cross-sectional study performed at the West China Hospital of Stomatology, Sichuan University, Chengdu, China. The study was approved by the Ethics Committee of the West China Hospital of Stomatology, Sichuan University. All patients provided a written informed consent and selected the inclusion/exclusion criteria in Table 1.

### Oral examination

The patients' oral hygiene habits were evaluated using a questionnaire.<sup>19</sup> Hygiene score was evaluated by the

**Table 1** Inclusion/exclusion criteria of patients.

Inclusion criteria	Exclusion criteria
1) Patients diagnosed with NPC stage T1N0M0 according to the 2003 TNM classification	1) Psychiatric disorders
2) The IMRT regimen was completed between January 2011 & December 2011	2) Patient received chemotherapy or traditional Chinese medicine
3) Aged 18–60 y	3) History of drug abuse
4) Before IMRT, patients had all permanent, adult dentition (28 teeth) with/without the 3 <sup>rd</sup> molars	4) Treatment with any drug known to affect the salivary glands or mouth mucosa in the past 3 mo
	5) Chronic systemic diseases
	6) Congenital diseases
	7) Smoking
	8) Alcohol addiction
	9) Recurrent NPC
	10) Received dental management during RT
	11) No fluoride was taken during IMRT

IMRT = intensity-modulated radiation therapy; NPC = nasopharyngeal carcinoma.

dentist examiner using a poor, fair, good, and very good ranking (1, 2, 3, and 4, respectively).<sup>20,21</sup> Xerostomia was also determined using a qualitative salivary gland performance analysis related to the subjective sensation of xerostomia (Table 2).<sup>22</sup>

### Measurement of salivary function

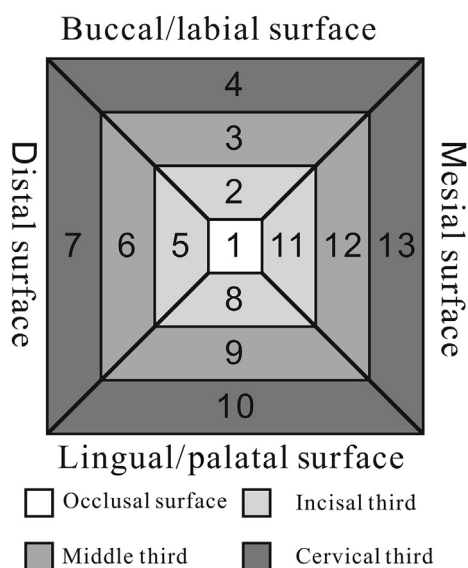
All saliva sample collections were conducted in the morning. Each patient was asked not to eat or drink for at least 2 hours prior to the sample collection. After resting for 5 minutes with no talking, patients were asked to chew on a piece of paraffin wax for 30 seconds and to expectorate directly into a graduated 50 mL sample collection tube on ice within 5 minutes.<sup>23</sup> The stimulated saliva flow rate was measured by dividing the volume of the saliva sample collection by 5 minutes. The pH value of the stimulated saliva was measured using a Metrohm digital pH meter (model: 632, Herisau, Switzerland).<sup>24</sup> Buffering capacity was measured using the dip-slide technique (CRT bacteria, Ivo-clar Vivadent, Germany) and classified following the manufacturer's instructions.<sup>25</sup>

### IMRT

All patients received a total dose of 65–72 Gy of high-energy X-ray radiation, 2 Gy/fraction.<sup>5,26</sup> The radiation fields were determined by the different size and location of NPC, all the teeth were located in the target center. These fractions were given during a 7-week period, 5 days per week. Treatment planning for all patients was performed using computerized treatment planning systems that incorporated three-dimensional beam modeling and calculation (Pinnacle: Koninklijke Philips Electronics N.V., Eindhoven, The Netherlands; Eclipse: Varian Medical Systems, Palo Alto, CA, USA; Xio: Elekta AB, Stockholm, Sweden).

### Radiation doses to the teeth

After IMRT, each premolar tooth crown for each patient was divided into 13 sites (Figure 1). Premolar teeth, but not molar teeth, were chosen for their more regular shape and smaller surface areas, as well as the shorter length in dental arch, which results in a more accurate outline drawing and the calculation of tooth exposure areas and dose. A medical physicist reviewed the patients' computerized treatment plans and imported the radiation dose distributions to the ADAC Pinnacle 3-9.0 planning system



**Figure 1** The 13 sites of the premolar tooth crown. The four surfaces of the crown (except the occlusal surface) are divided into three parts: the incisal third, the middle third, and the cervical third. 1 = occlusal surface; 2 = incisal third of buccal/labial surface; 3 = middle third of buccal/labial surface; 4 = cervical third of buccal/labial surface; 5 = incisal third of distal surface; 6 = middle third of distal surface; 7 = cervical third of distal surface; 8 = incisal third of lingual/palatal surface; 9 = middle third of lingual/palatal surface; 10 = cervical third of lingual/palatal surface; 11 = incisal third of mesial surface; 12 = middle third of mesial surface; 13 = cervical third of mesial surface.

(ADAC Laboratories, Milpitas, CA, USA). A dentist drew the outline of the every premolar tooth, then the medical physicist calculated the estimate radiation dose per tooth site using the Pinnacle system.<sup>27</sup> The mean dose delivered to each premolar tooth was determined on the treatment planning system.

We subsequently divided the individual tooth radiation dose into seven categories as: Group A (no exposure-19 Gy); Group B (20–29 Gy); Group C (30–39 Gy); Group D (40–49 Gy); Group E (50–59 Gy); and Group F (> 60 Gy).

### Evaluation of the teeth

The severity of tooth damage was clinically scored by three dentist examiners (Kappa = 0.69), blinded to the levels of

**Table 2** Oral examination of the patients.

		Mean ± SD	Range
Salivary function	Stimulated saliva flow rate (mL/min)	0.66 ± 0.27	0.05–0.9
	Saliva pH	—	6.77–7.40
	Saliva buffering capacity	High	—
Oral hygiene habits	Frequency of brushing (times/d)	—	1–2
	Clinical application of fluoride products	None	—
	Use of saliva substitutes	None	—
	Preference of food	None	—

SD = standard deviation.

radiation exposure, using a previously validated index to assess post-RT damage.<sup>7</sup> If two of the three scores were the same, then the score of the same two would be used, and the average score would be used if the three scores were different. Based on the magnitude of the tooth score, the tooth site was subsequently categorized as having no damage (0), slight damage (1), moderate damage (2), or severe damage (3) for statistical analysis (Table 3).

## Statistical analysis

Descriptive statistics were used to characterize the patient population. A mixed-effect logistic model was fitted to assess the effect of the tooth-level radiation dose regarding tooth damage at different sites. The relationship between dose distribution and the caries severity score was analyzed by means of logistic models and Tukey's honestly significant difference *post-hoc* test. Statistical analysis was performed using SAS 8.2 (SAS Institute, Cary, NY, USA). A P value < 0.05 was considered significant. Patients were treated as random effect with tooth dose, xerostomia and oral hygiene treated as fixed effects.

## Results

### Characteristics of the patients and teeth

Ninety-seven patients were eligible to this study, but 55 patients were excluded (29 refused to participate, 21 were lost of follow-up, and 5 did not complete the full IMRT regimen). Finally, 42 patients were included, aged 24–59 years (mean age, 46 years). All patients received 70.0 Gy, with doses to individual premolar tooth sites varying widely within and between patients from 28.20 Gy to 50.85 Gy.

### Oral health information

The general oral health habits and the salivary function of the patients are presented in Table 2. None of the patients had clinical use of fluorine products or artificial saliva. Furthermore, no special food preferences were observed. Xerostomia was reported by 32 patients (76.19%). The saliva pH ranged from 6.77 to 7.40, which is in line with reported normal salivary pH range (5.3–7.8).<sup>28</sup> The stimulated saliva

**Table 3** Surface score index.<sup>7</sup>

Damage	Score	Description
None	0	No change in tooth surface. Appearance is shiny, smooth, & intact.
Slight	1	Single focal area of enamel/tooth structural loss ( $\leq 2$ mm in diameter). Surface may also be marked with a white line &/or brown stain.
Moderate	2	Focal area of single enamel/tooth structural loss ( $\sim 2$ mm in diameter).
Severe	3	Extensive enamel/tooth structural loss interlinked with the pulp cavity.

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**Table 4** Odds ratios and 95% confidence intervals for predictors of tooth damage.

Tooth dose (Gy)	Caries (n; %)	OR	95% CI	P
0–19	—	—	—	—
20–29	209; 15.99	3.87	(2.08, 7.21)	0.0037*
30–39	697; 36.11	12.55	(6.80, 23.16)	0.0029*
40–49	494; 65.00	48.32	(25.84, 90.34)	0.001*
50–59	102; 90.27	200.17	(82.38, 486.39)	0.0001*
$\geq 60$	6; 100	116.60	(12.90, 1000)	0.0001*
Covariates				
Oral hygiene score		0.89	(0.79, 1.03)	0.653
Xerostomia		1.07	(0.88, 1.41)	0.517

CI = confidence interval; OR = odds ratio.

\* Statistically significant.

flow rate ranged from 0.05 to 0.9, which is far lower than the lowest normal standard, reported to be 2.0 mL/min.<sup>29</sup> The covariates of xerostomia and oral hygiene scores are displayed in Table 4.

### Tooth damage

Among all patients, 334 premolar teeth with 4342 sites were clinically evaluated. Overall, 99.4% of remaining premolar teeth and 37.7% of sites exhibited damage, with the remaining sites having no damage.

### Predictors of radiation caries

The odds ratios and 95% confidence intervals for the logistic model predicting radiation caries are detailed in Table 4. A similar approach was used regarding the patient level variables, xerostomia, and oral hygiene habits. These covariates were included in the model to statistically adjust for the unique effect of tooth-level dose in Table 4. The effect of increasing doses of radiation at the premolar tooth level significantly and independently predicted slight, moderate, or severe tooth damage at radiation doses > 30 Gy (odds ratio = 12.53). The odds of developing damage in the 40–50 Gy and > 60 Gy radiation dose categories were 12–200 times greater than in the 0–19 dose category. However, for teeth exposed to 50–59 Gy (compared with 0–19 Gy) the odds of tooth damage occurring was greater by a factor of 200.17 (95% confidence interval: 82.38–486.39).

**Table 5** Caries scores and tooth radiation dose exposures.

Caries score (group)	Radiation dose (Gy)	Total no.	P
0 (A)	30.35 $\pm$ 7.23	2706	
1 (B)	35.83 $\pm$ 6.78*	894	0.023
2 (C)	43.89 $\pm$ 8.16*	701	<0.0001
3 (D)	44.11 $\pm$ 12.00*	41	<0.0001

\* Significant differences versus Group A (caries score = 0; P < 0.05).

Radiation caries were classified according to the caries score. Compared with score 0, teeth with scores of 1, 2, or 3 received significantly more radiation (0:  $30.5 \pm 7.2$  Gy vs. 1:  $35.8 \pm 6.8$  Gy, 2:  $43.9 \pm 8.2$  Gy, and 3:  $44.1 \pm 12.0$  Gy, all  $P < 0.05$  vs. score 0). However, there was no difference between teeth with scores 1, 2, or 3. The results also indicated that radiation caries were prone to develop when the radiation dose was  $> 35.8$  Gy (Table 5).

## Discussion

IMRT is noted for less toxicity than RT, but the exact dose associated with tooth damage is mostly unknown. The objective of this study was to evaluate the severity of dental lesions after IMRT and the correlation with the radiation dose to the dentition in patients with NPC. Results showed that among 4342 sites from 334 premolar teeth, the odds of developing caries damage were 12–200 times greater for teeth exposed to 30–60 Gy compared with teeth unexposed to RT. A new radiation caries lesion was likely to occur when the dose was  $> 35.8$  Gy after 17 days' RT.

Breakdown of the dentition following RT tends to start within the 1<sup>st</sup> year and becomes more severe with time.<sup>16</sup> While the relationship between RT and dental decay is well documented,<sup>5,9</sup> it is important to note that post-radiation dental lesions differ considerably in clinical appearance, pattern of development, and progression from the dental decay seen in nonirradiated patients. Typical dental decay occurs in pits, fissures, and proximal areas between the teeth.<sup>30</sup> By contrast, post-RT dental lesions tend to occur in the cervical (junction between crown and root) and cuspal areas.<sup>5,31</sup> Many factors contribute to the deterioration of the dentition following RT. Consequently, in our return visit, some NPC patients reported that they failed to follow doctors' order to use the fluoride gel for unknown reason. As previous literature has demonstrated the importance of fluoride products in dental caries prevention,<sup>12</sup> the patients that did not use the fluoride gel were selected in our study to ensure consistency. We exclusively selected patients with NPC to obtain a more uniform RT field range and dose.

To date, the present study is the first in which the individual tooth surface has been divided into 13 sites according to the anatomy of the tooth, and in which the radiation dose of each site was evaluated and subsequently associated with post-RT tooth damage. To allow the wide variety of follow-up intervals in the study population, we set the elapsed time as having an upper limit of 48 months. Xerostomia and oral hygiene habits were included in the model as covariates. The current findings coupled with the unique clinical presentation of the post-RT lesions suggest a direct effect of radiation on tooth structure that increased with radiation dose. Thirty gray units is the salivary gland threshold; beyond this level of radiation the damage to the glands is permanent.<sup>11</sup> Between 30 Gy and 60 Gy, the 12–200 increase in the odds of developing tooth damage is likely to be related to the impact of RT on the salivary glands and the loss of the protective effects of the saliva. However, even at doses of 30–60 Gy, initial tooth breakdown commences with enamel shear fracture at loading and flexure sites, suggesting a possible change in tooth

structure. A previous *in vitro* study has shown that when teeth are dried, increased strain occurs at the dentino-enamel junction, decreasing the stability of the enamel-dentine interface.<sup>32</sup>

At doses  $> 50$  Gy, a potential explanation for the exponential increase in the odds of tooth damage can be found in previous reports involving *in vitro* radiation-induced changes in tooth structure.<sup>6–8</sup> These studies used radiation doses  $> 50$ –60 Gy and reported changes in the properties of dentine and enamel including a decrease in hardness, elastic modulus, and tensile strength, as well as increased susceptibility to enamel shear fracture. These changes in the properties of dentine and enamel and the associated reduction in bond strength between them following exposure to a high radiation dose *in vitro* could possibly help explain the occurrence of enamel delamination at loading and flexure sites in patients after RT.<sup>11,31</sup>

Collectively, it appears that postradiation tooth damage is potentially mediated by saliva loss and direct tooth effects from radiation, with an additive impact as the total dose increases. In our study, salivary function was measured through stimulated flow rate, saliva pH, buffering capacity,<sup>33</sup> and xerostomia qualitative.<sup>22</sup> Literature related to post-RT dental disease is dominated by the effects of xerostomia<sup>5,16</sup> and IMRT-treated patients still commonly experienced loss of salivary function.<sup>34</sup> However, because xerostomia was reported by the vast majority of patients (76.19%), there was minimal variability, and thus, it is not surprising that it was not a predictive component. The data of our study show that stimulated saliva flow rate of NPC patients do not recover to their baseline 3 years after IMRT, which was also reported in several publications.<sup>33,35</sup> Notably, there are no significant decreases in saliva pH, buffering capacity, and the xerostomia scores. The pH value of stimulated saliva in our study ranged from 6.77–7.40, which is in line with the reported normal pH between 5.3 and 7.8.<sup>28</sup> It is interesting to note that some researchers have reported a decrease in saliva pH from 7.0 to 5.0 in combination with a loss in buffering capacity immediately after RT.<sup>5,36</sup> As salivary flow gradually increases with time after RT, the mean salivary pH improves to 6.9 after 1 year and recovered to 7.2 at 2 years after IMRT. Additionally, the proportion of RT patients showing saliva with medium-to-high buffering capacity increases to 70.6% at 1 year post-RT and to 85.7% at 2 years' post-RT.<sup>33</sup> Hence, a new buffering system may become established approximately 1 year after IMRT. However, since the salivary flow rate is not yet recovered in our study from those who are 36–48 months post-RT, it is possible to conclude from the given data that salivary function is still damaged. In our study, there appears to be a 12–200 times increase in tooth damage between 30–60 Gy that is likely related to salivary gland impact as already described. Significant reduction in parotid gland function (Grade 3 or 4 on RTOG/EORTC LENT-SOMA scale) has been reported after a mean dose of 25–32 Gy.<sup>37,38</sup> Analysis of normal tissue complication probability models for post-RT on parotid gland function demonstrated a  $TD_{50}$  of 38–40 Gy.<sup>39,40</sup> Submandibular gland tissue may be more radioresistant, but the threshold for maintaining gland function is still lower (approximately 40 Gy) than the suggested direct tooth damage radiation threshold of  $\geq 60$  Gy.<sup>41,42</sup>



Data of the present study suggest a continuous dose-response relationship at doses > 30 Gy after 15 days' RT, and a new RT-induced caries lesion was prone to develop when the radiation dose was higher than 35.8 Gy after 17 days' RT. Therefore, it might be beneficial to maintain the tooth exposure dose as low as possible. These dose constraints apply to each individual tooth. However, a better understanding of the effects of RT on mineralized tooth substrates is required.

The present study does have its limitations. The sample size was small and from a single center. In addition, its retrospective nature prevented us to assess factors that were not recorded as the usual assessment of the patients. Further study is needed to capture more data throughout the treatment planning process and to evaluate the effects of RT on the mechanical properties, chemical structure, and function of enamel and dentine before and after IMRT.

## Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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