Original Article

Benefits of intraoral stents for sparing normal tissue in radiotherapy of nasopharyngeal carcinoma: a radiobiological model-based quantitative analysis

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Background: To determine the value of individualized intraoral stent for normal tissue sparing in radiotherapy of nasopharyngeal carcinoma (NPC) using quantitative analysis of radiobiological model.

Methods: Sixteen patients with NPC who used intraoral stent and 17 patients without intraoral stent were enrolled in this study. All patients underwent Helical Tomotherapy (HT) in our center. Based on the patient's dose volume histogram (DVH), the modified Webb-Nahum model was used to predict tumor control probability (TCP), and the parallel architecture model and Lyman-Kutcher-Burman (LKB) model were used to estimate the normal tissue complications probability (NTCP). The differences of TCP, NTCP and dosimetric parameters between the two groups were compared and analyzed.

Results: The mean dose metrics of oral cavity, mandible, left and right parotid gland in patients with intraoral stent was significantly decreased by 11.6%, 12.2%, 15.4%, and 8.7% on average, respectively ($P<0.05$), while the conformity index (CI, $P=0.056$) and homogeneity index (HI, $P=0.676$) of the tumor target showed no statistically different. Quantitative assessment of radiobiological model revealed that the NTCP of oral cavity and parotid glands were both significantly lower in patients with intraoral stent than those without intraoral stent ($P<0.001$), without compromising TCP of the tumor target ($P=0.056$). For example, patients using intraoral stent significantly reduced oral mucositis and xerostomia complication probability by 2.52% and 10.11% on average compared to unused ones, respectively.

Conclusions: The custom-made intraoral stents showed promising value at sparing normal tissue during radiotherapy for NPC without affecting target dose coverage or tumor control.

Keywords: Custom-made intraoral stent; radiotherapy; tumor control probability (TCP); normal tissue complications probability (NTCP); nasopharyngeal carcinoma (NPC)

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Introduction

Nasopharyngeal carcinoma (NPC) is a kind of head and neck cancers which is particularly prevalent in southern China and Southeast Asia (1). Radiotherapy (RT) plays an efficient role in the treatment of NPC with successful results (2). However, radiation-induced injury has still been observed and is frequently associated with normal tissue complications, which may affect prognosis for patients and reduce quality of life (3-5). Although advances in intensity-modulated radiotherapy (IMRT) have allowed greater sparing of normal tissues, yet oral-related injuries remain a major challenge and, therefore, several strategies have been adopted to reduce the risk of oral complications.

Recent studies have documented the advantage of using intraoral stent and other similar devices for accurate positioning during RT and sparing normal adjacent tissue (6,7). Using this device can increase the distance between the mandible and the maxilla, thus minimizing the risk of radiation-induced complications in normal oral tissue (8). By analyzing the dosimetric parameters, prior studies have found that intraoral stent was effective in decreasing dose to normal tissues (9-11). However, it is difficult to quantify the radiation-induced toxicities by a dosimetry analysis alone.

Radiobiological model, which uses the dose-volume histogram (DVH), allows for quantification of normal tissue complication probability (NTCP) (12-15) and is widely used in clinical decision making (16), treatment technique selection (17), and planning optimization (18). However, few studies have attempted to quantify the benefit of intraoral stent at normal tissue sparing by using these radiobiological models. Therefore, the purpose of our study was to quantify the effect of intraoral stent on radiation-induced normal tissue toxicity and tumor control probability (TCP) in patients with NPC receiving concurrent chemo-radiotherapy (CCRT) using radiobiological model analysis. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tcr-21-1324).

Methods

Patient characteristics

The eligibility criteria for patient enrollment are as follows: (I) biopsy-proven NPC; (II) Helical Tomo radiotherapy (RT) was administered at Nanjing Drum Tower Hospital; (III) completion of planned RT treatment; (IV) plan CT and RT dose data at enrollment were available. Between October 2015 and July 2020, a total of thirty-three patients with NPC who underwent Helical Tomo radiotherapy at Nanjing Drum Tower Hospital were evaluated and divided into 2 groups: with intraoral stent (group 1, n=16) and without intraoral stent (group 2, n=17). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Nanjing Stomatological Hospital, Medical School of Nanjing University (No. NJSH-2021NL-041) and individual consent for this retrospective analysis was waived.

For group 1 (with intraoral stent), the NPC patients wearing a customized intraoral stent during RT are the protocol implemented by our center from November 2019.

For group 2 (without intraoral stent), the NPC patients who did not wear an intraoral stent due to limitations (e.g., trismus or limited jaw opening) or patients received RT before November 2019.

The patient general characteristics were described in *Table 1*.

Construction of the custom-made intraoral stent

Construction of the custom-made intraoral stent contained the following steps, which were applied to the patient cohort receiving it. Firstly, oral examinations were performed and unretainable decayed teeth were extracted. The maxillary and mandibular impressions were then taken from the patients' dentitions. Next, wax occlusal dike was used to transfer maxillo-mandibular relationship. Subsequently, the wax patterns were made on the articulator. Finally, after packing, plastic filling, curing, and polishing, the production customized intraoral stent was completed. *Figure 1* showed the customized intraoral stent used in patients with NPC.

Target delineation and IMRT planning

Patients were placed in supine position and immobilized using a thermoplastic mask against head and shoulder. Planning CT scans were performed by a Siemens SOMATOM Definition CT scanner (Siemens, Ehrlangen, Germany) using standard scan parameters: 120 kVp, 120 mA, 5 mm slice thickness, 0.8×0.8 pixel spacing. The acquired CT images were transferred to MIM Meastro (MIM Software, Inc., Cleveland, OH, USA) and the regions of interest were contoured.

The contrast-enhanced CT and magnetic resonance (MR) images were fused to the planning CT images and the

Table 1 Baseline characteristics of 33 patients with NPC

Characteristic	Patients with oral stents (n=16)	Patients without oral stents (n=17)	P
Gender			0.605
Male	12	14	
Female	4	3	
Age (years)			0.215
Median [range]	52 [29–75]	47 [23–68]	
AJCC staging			0.576
III	13	15	
IVa	3	2	

NPC, nasopharyngeal carcinoma.

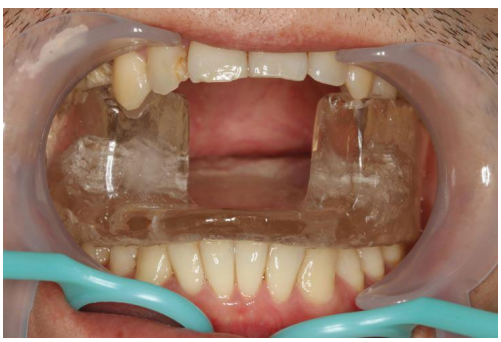

Figure 1 The customized intraoral stent used in radiotherapy of patients with NPC. NPC, nasopharyngeal carcinoma.

targets were delineated by both experienced radiologists and radiation oncologists. The delineation principle of tumor target was the same as those described in our previous work (19). The gross tumor volume (GTV) including the primary tumor and involved lymph nodes identified by imaging, clinical examination, as well as endoscopic findings. The clinical target volume (CTV) was determined to include regions that have a high risk of microscopic tumor involvement. The planning target volume (PTV) was constructed by adding an additional margin of 3–5 mm to the CTV according to the immobilization and localization uncertainties.

IMRT was administered using Helical Tomotherapy (HT), for which plans were designed by Tomo treatment planning system (Accuray, Inc., USA). The doses were prescribed to cover at least 95% of PTV while meeting the dose constraint for organs at risk (OAR) (20). All HT plans were optimized with the same prescription dose and same dose constraint for OARs.

Dosimetry analysis

For PTVs, the conformity index (CI) and homogeneity index (HI) were used to compare two groups of HT plans (with or without intraoral stent) (21,22).

For OARs, mean dose (D_{mean}) to mandible, temporal-mandibular joint (TMJ), parotid, and submandibular gland were recorded for the two groups. Besides, according to Eisbruch *et al.* (23), the surfaces of the inner lips, buccal mucosa, tongue, base of tongue, floor of mouth, and palate were countered as a distinct organ, namely the oral cavity. The mean dose to the oral cavity was also evaluated and recorded.

TCP and NTCP

Differential dose volume histogram (DVH) at 0.01 Gy interval of each patient was exported to RADBIOMOD version 0.3b (14) for TCP and NTCP calculations.

TCP calculation

The TCP was calculated using the modified Webb-Nahum model by Avazon *et al.* (24), which is based on Poisson statistics and the linear-quatratic (LQ) model. The model assumes the number of clonogens in the tumor is Poisson-distributed and calculates the probability of no viable clonogens left after a course of RT. The model can be described as follows:

$$\mathrm{TCP} = \frac{\mathrm{I}}{\sigma_a\sqrt{2\pi}}\int_0^{\infty}\prod \exp \left\{-\rho(T)V_i \exp\left[-\alpha\cdot D_i\cdot\left(1+\frac{\beta}{\alpha}\cdot d_i\right)\right]\right\} \cdot \exp\left[-\frac{(\alpha-\bar{\alpha})}{2\sigma_\alpha^2}\right]\mathrm{d}\alpha \quad [1]$$

$$\rho(T) = \rho_0 \cdot 2^{((T-T_k)/T_{pot})} \quad [2]$$

$$\alpha_H = \alpha_A / OER \quad [3]$$

$$(\alpha/\beta)_H = (\alpha/\beta)_A \cdot OER \quad [4]$$

$$\mathrm{TCP} = \mathrm{TCP_h}(HF) + \mathrm{TCP_a}(1-HF) \quad [5]$$

The meanings and sources of the parameters used in this TCP model are summarized in *Table 2*.

NTCP calculation

We adopted a parallel architecture model (25) fitted by Bhide *et al.* (12), to calculate the NTCP of the oral cavity. The LKB models fitted by Burman *et al.* (26) and Semenenko *et al.* (27), were employed to calculate the NTCP of the parotid gland and TMJ, respectively.

The parallel architecture model is a logistic function and described as follow:

$$NTCP_{parallel} = \frac{1}{1+(\frac{TD_{50}}{D})^{k}} \quad [6]$$

The LKB model consisting of three equations:

$$NTCP_{LKB} = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} e^{\frac{-x^2}{2}} dx \quad [7]$$

$$t = \frac{D_{eff} - TD_{50}}{m \cdot TD_{50}} \quad [8]$$

$$D_{eff} = \left(\sum_i v_i D_i^{1/n}\right)^n \quad [9]$$

Details about the meanings and sources of these parameters can be seen in *Table 3*.

Table 2 Radiobiological parameters used for TCP calculation

Parameters (unit)	Average value of uniform distribution
α(Gy^{-1})	0.33
σ_α(Gy^{-1})	0.07
α/β(Gy)	10
ρ(cm^{-3})	10^7
T_k(days)	28
T_{pot}(days)	3
HF	0.22
OER	1.5
Dose per fraction (Gy)	2
Fractions/week	5
Prescription dose (Gy)	70

α and β, intrinsic radiosensitivity parameters of tumor cell in hit of single-hit and double-hit effect; σ_α, standard deviation of α; ρ, clonogenic cell density; T_k, kick-off time; T_{pot}, potential doubling time; TCP, tumor control probability; HF, hypoxic fraction; OER, oxygen enhancement ratio. The values listed in this table are sourced from Avanzo *et al.* (24).

Statistical analysis

Statistical analysis was performed using unpaired Mann-Whitney U test by statistical software GraphPad Prism version 8.3.0 (GraphPad Software Inc., San Diego, CA, USA), to compare 2 groups. P<0.05 was considered statistically significant.

Results

Comparison of CI and HI of the tumor target

As shown in *Table 4*, the differences in CI and HI between the two groups (with *vs.* without intraoral stent) were not statistically significant (CI, P=0.056; HI, P=0.676), which

Table 4 CI and HI parameters of PTV between the two groups

Parameters	Patients with oral stents	Patients without oral stents	P
CI	0.863±0.032	0.844±0.021	0.056
HI	0.105±0.145	0.067±0.014	0.676

CI, conformity index; HI, homogeneity index; PTV, planning target volume.

Table 3 Radiobiological parameters used for NTCP calculation

OAR	LKB model parameters			Parallel model parameters		Clinical endpoint	α/β
	n	m	TD_{50}	k	TD_{50}		
Parotid	1	0.53	31.4Gy	–	–	Xerostomia expressed as reduction in stimulated salivary flow at 6 months after radiotherapy (26)	3 (27)
TMJ	0.07	0.1	72 Gy	–	–	Marked limitation of joint function (25)	2 (26)
Oral cavity	–	–	–	1	51 Gy	Grade 3 oral mucositis (12)	10 (12)

NTCP, normal tissue complications probability; OAR, organ at risk; n, volume dependence of the complication probability; m, slope of the dose-response curve; TD_{50}, dose at which 50% of patients experience toxicity; k, slope of the dose-response curve. The values listed in this table are sourced from Semenenko *et al.* (27), Burman *et al.* (26), and Bhide *et al.* (12).

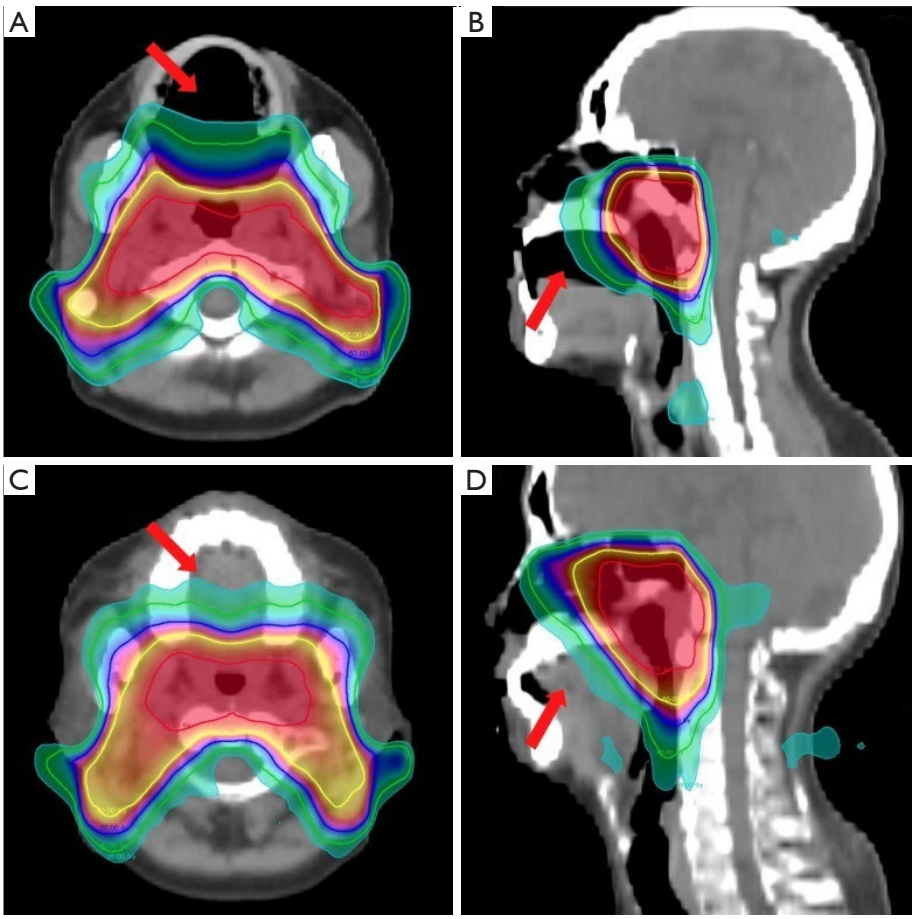

Figure 2 CT scans and dose distributions of patients with and without intraoral stent for radiation planning. (A,B) Transverse and sagittal section of a patient with the intraoral stent; (C,D) transverse and sagittal section of a patient without intraoral stent. For patient with oral stent (A,B), red arrow showed the tongue was separated from the radiation field. For patient without oral stent (C,D), red arrows show the tongue was involved in the radiation field.

means that intraoral stent has no significant effect on target dose distribution. *Figure 2* shows the dose distribution of tumor target.

Comparison of dosimetry metrics of the critical structures

The dosimetry metrics of critical structures are summarized in *Table 5*. Compared with patients without intraoral stent, the mean dose (D_{mean}) to oral cavity, mandible, and bilateral parotid were significantly lower in patients use intraoral stent (P<0.05 for all). The D_{mean} of bilateral TMJ and submandibular glad was slightly lower in patients with intraoral stent, although it did not reach statistical significance (*Table 5*, *Figure 3*).

Comparison of TCP of the tumor target and NTCP of the critical structures

In *Figure 4*, as well as *Table 6*, we show the results of TCP and NTCP analysis. For TCP of tumor targets, no statistically significant differences were observed between the two groups (P=0.056), indicating that whether or not to use an intraoral stent has no significant effect on tumor control. As shown for NTCP, complication probability of oral cavity (P<0.001) was significantly decreased in patients with intraoral stent, and there was also a strong trend toward a decrease in parotids (P<0.001). Furthermore, in NTCP analysis of bilateral TMJ, no statistical differences were observed (P=0.841).

Table 5 Dosimetric parameters of OARs between the two groups

OAR	Patients with oral stents (D_{mean}, Gy)	Patients without oral stents (D_{mean}, Gy)	P
Oral cavity	32.98±1.91	37.31±2.79	<0.001†
Mandible	34.63±3.22	39.46± 2.52	<0.001†
TMJ-L	38.64±7.01	42.71±4.75	0.072
TMJ-R	36.92±7.63	39.17±4.07	0.213
Parotid-L	30.4±3.33	35.93±4.17	<0.001†
Parotid-R	29.42±2.25	32.25±2.36	0.001†
Submandibular gland-L	54.01±7.09	56.40±6.77	0.443
Submandibular gland-R	52.33±6.74	55.73±5.86	0.191

†, P<0.05 were considered significant. OAR, organ at risk; D_{mean}, mean dose; TMJ-R, right temporal-mandibular joint; TMJ-L, left temporal-mandibular joint.

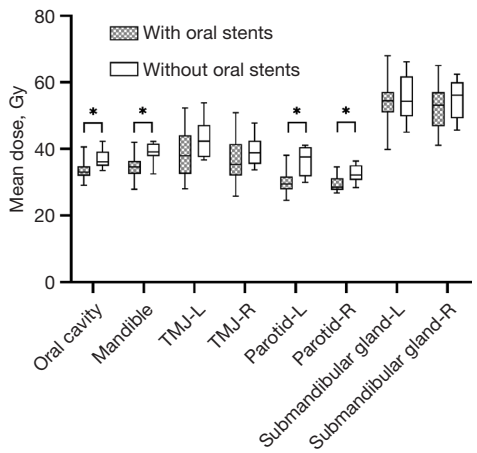

Figure 3 Box plots of the mean dose (Gy) for the two groups on each location, showing a decreasing trend in radiation dose to adjacent normal tissue, especially for oral cavity (P<0.001), mandible (P<0.001), left parotid (P<0.001), right parotid (P=0.001). *, P<0.001.

Discussion

Radiation-induced oral complications are common and significantly affect the quality of life of patients. Prior work has documented the effectiveness of an intraoral stent in reducing oral-related toxicity in head and neck cancer patients treated with radiotherapy. The major advantages of the intraoral stents were reproducible positioning and minimizing the radiotoxicity of normal structures. Feng *et al.* (11) and Verrone *et al.* (8,9), for example, report that wearing an intraoral stent can effectively reduce the dose to oral tissues. However, few studies have quantitatively assessed the effect of wearing intraoral stents on complication risk and tumor control rate based on dose-response analysis. Quantitative descriptors of dose-response curve can be generated by radiobiological models and used for comparison between different regimens (e.g., with or without intraoral stents). In this study, we adopted the radiobiological models, including the LKB (26,27) and parallel architecture (12) NTCP models, as well as the modified Webb-Nahum TCP model (24), to quantitatively explore the value of customized intraoral stent for sparing normal tissue during radiotherapy for NPC.

The method used in previous work for evaluating the benefits of oral stents is to assess the dosimetric parameters derived from the DVH (e.g., D_{mean}) (8,9,11). In agreement with previous work, dosimetric analysis of this study showed that patients who wore the intraoral stent had a decreasing trend in radiation dose to adjacent normal tissue, especially for oral cavity, mandible and bilateral parotid, which may be due to the intraoral stent increased distance between the mandible and the maxilla. In addition, the dose distribution characteristics (CI and HI), showed no significant differences between the two groups, suggesting that customized intraoral stent showed no significant effect on target dose coverage. However, this sole assessment of dosimetric parameters is a very simple method to quantify the effect of intraoral stents and has some limitations. Namely the previous studies were unable to make full use of DVH and radio-sensitivity factors to evaluate the reduction of radiotoxicity burden and the impact of tumor control by using intraoral stents.

Radio-biological models have been proposed as a way to overcome these limitations. In this work, we applied radiobiological models to investigate the protective

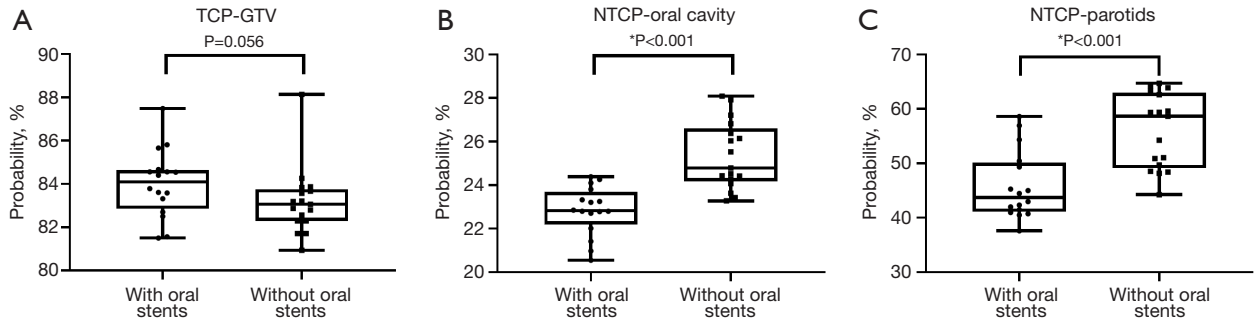

Figure 4 Box plots for the value of radiobiological models, showing that the intraoral stent was effective for reducing the risk of complications (especially for oral cavity and left parotid) without compromising tumor control. (A) TCP of GTV (P=0.056); (B) NTCP of oral cavity (P<0.001); (C) NTCP of parotids (P<0.001). TCP, tumor control probability; GTV, gross tumor volume; NTCP, normal tissue complications probability.

Table 6 TCP and NTCP values between the two groups

Structure	Patients with oral stents (%)	Patients without oral stents (%)	P
TCP			
GTV	84.02±1.57	83.18±1.56	0.056
NTCP			
Oral cavity	22.83±1.12	25.35±1.55	<0.001†
TMJ	0.43±0.53	0.22±0.62	0.841
Parotids	45.83±6.30	55.94±6.85	<0.001†

†, P<0.05 were considered significant. TCP, tumor control probability; NTCP, normal tissue complications probability; GTV, gross tumor volume; TMJ-R, right temporal-mandibular joint; TMJ-L, left temporal-mandibular joint.

value of wearing intraoral stent. As for the comparison of oral mucositis risk between the two groups, we used the parallel architecture model, which assumed that the organ (e.g., oral cavity) consist of numerous subunits that respond to radiation independently. The model is defined as a sigmoid function that describes the probability of damaging a subunit at a given bioequivalent dose. We found that patients wearing intraoral stent significantly reduced grade 3 oral mucositis complication probability by 2.52% on average compared to unused ones ($NTCP_{mean}$: 22.83% *vs.* 25.35%). Similar to parallel architecture model, the LKB model is also widely used for assessing the radiotoxicity and the model parameters are available from the previous work. The result showed that the incidence of xerostomia for parotids were significant lower in oral stents group than in the control group, achieved a reduction of 10.11% ($NTCP_{mean}$: 45.83% *vs.* 55.94%). Apart from NTCP analysis, a Webb-Nahum Poisson TCP model was employed for assessing the tumor control of the two groups. The Webb-Nahum model assumes that the number of surviving clonogens is Poisson-distributed, by which the probability of no surviving clonogens in the tumor after radiotherapy could be calculated. In this work, we choose a modified Webb-Nahum model that incorporates additional radiobiological factors including radiosensitivity, hypoxia, and repopulation. Our findings showed that wearing the intraoral stent is independent of tumor control (P>0.05). In this way, instead of assessing multiple dosimetric parameters, a single NTCP and TCP indicators could be used to quantify the advantage of wearing an intraoral stent. These radiobiological indicators could replace the dosimetric parameters in order to closely reflect the clinical goals of using oral stents in radiotherapy.

In clinical practice, the goal of radiotherapy plan evaluation is to achieve the best compromise, including a low complication probability value (NTCP) and a high TCP. The findings of this study extend the previous work (8,9,11), confirming that the intraoral stent was effective for reducing the risk of oral complications without compromising tumor control. Most notably, this is the first study to our knowledge to investigate the protective value of wearing intraoral stent using radiobiological models. Our results provide quantitative evidence for the value of intraoral stent at sparing normal tissue and suggest that this device appears to be effective in normal tissue protection for patients with NPC during radiotherapy.

Several limitations are worth noting in present study, namely its retrospective study design in small sample size

and the sample was not reassessed once after the end of treatment. Future study should therefore include follow-up work designed to evaluate the patients' quality of life and validate performance of the radiobiological model in a large cohort. In addition, radiobiological models published by other groups contain different types and parameters, each of which may affect the prediction result and limit their generalizability. Besides, although the IMRT plans with or without oral stents were designed by the same experienced physicist (Juan Liu) using the TomoTherapy treatment planning system, the degree of familiarity and techniques of planning skills would refine gradually as time progresses, which may have a potential impact on dosimetry results.

Despite these current challenges and limitations, the potential for intraoral stents is immense. It is widely recognized that benefits associated with wearing intraoral stent for radiotherapy is evident. Moreover, the radiobiological models could be useful in estimating the reduction of radiotoxicity burden that might be guided as part of tumor dose escalation protocols.

In conclusion, radiobiological model analysis demonstrated the potential value of custom-made intraoral stent at reducing complication risk during radiotherapy for NPC without compromising target dose coverage or tumor control.

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Footnote

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Data Sharing Statement: Available at https://dx.doi.org/10.21037/tcr-21-1324

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/tcr-21-1324). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Nanjing Stomatological Hospital, Medical School of Nanjing University (No. NJSH-2021NL-041) and individual consent for this retrospective analysis was waived.

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