



# Superficial parotid lobe–sparing delineation approach: a better method of dose optimization to protect the parotid gland in intensity-modulated radiotherapy for nasopharyngeal carcinoma

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## ABSTRACT

### Purpose

We used a superficial parotid lobe–sparing delineation approach for dose optimization with better protection for the parotid glands in intensity-modulated radiotherapy (IMRT) for nasopharyngeal carcinoma (NPC) patients.

### Methods

Compared with traditional contouring of the entire parotid glands as organs at risk (OARS) in IMRT for NPC, we used a superficial parotid lobe–sparing delineation approach of contouring the superficial parotid lobes as OARS. Changes in dose to the parotid glands, the targets, and other OARS were evaluated.

### Results

The mean dose to the parotid glands overall decreased by more than 4 Gy in the test plans. Impressively, the mean dose to the superficial parotid lobes in the test plans was not more than 30 Gy, regardless of clinical stage. In T1–3 NPC patients, the dose distributions for targets were not significantly different in the control plans and the test plans. However, for some T4 patients, the dose distributions for targets and brainstem in the test plans could not meet clinical requirements.

### Conclusions

The superficial parotid lobe–sparing delineation approach can significantly lower the mean dose to the entire parotid and to the superficial parotid lobe in T1–3 NPC patients, which would be expected to

result in less xerostomia and better quality of life for those patients.

### KEY WORDS

Intensity-modulated radiotherapy, nasopharyngeal carcinoma, superficial parotid lobes

## 1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) is one of the most commonly diagnosed head-and-neck malignancies in Southeast Asia, and radiotherapy is the main treatment. During radiotherapy treatment, the salivary glands on both sides usually receive a high dose of radiation. As a result, patients experience long-term xerostomia: dry mouth, sore throat, altered taste, dental decay, changes in voice quality, and impaired chewing and swallowing<sup>1–5</sup>. Yeh *et al.*<sup>6</sup> reported that 87.8% of NPC patients (745 of 849) had xerostomia after conventional radiotherapy. In recent years, intensity-modulated radiotherapy (IMRT) has relieved this problem to some extent. Kam *et al.*<sup>7</sup> compared the incidence of severe xerostomia in 56 early-stage NPC patients, of whom 28 received conventional radiotherapy, and 28 received parotid-sparing IMRT. One year after treatment, the authors found that, compared with patients in the conventional radiotherapy group, those in the IMRT group had a significantly lower incidence of observer-rated severe xerostomia (39.3% vs. 82.1%,  $p = 0.01$ ) and a higher parotid salivary flow. Hsiung *et al.*<sup>8</sup> also reported that IMRT could significantly preserve parotid gland function for NPC patients.

The parotid is the largest salivary gland in humans, producing about 60%–65% of stimulated saliva. Damage to this gland plays an important role in the generation of xerostomia. The parotid is highly sensitive to radiation: in the first week of conventional radiotherapy, salivary flow decreases by 50%–60%; after 7 weeks of conventional radiotherapy, salivary flow diminishes to approximately 20% of that before

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treatment<sup>9</sup>. Consensus is that a mean dose to the parotid of less than 26–30 Gy can preserve its function substantially<sup>10,11</sup>; however, Zhao *et al.*<sup>12</sup> reported that the mean dose to the parotid in NPC patients receiving IMRT was about 36.5 Gy. A parotid dose limitation of less than 26–30 Gy is hard to achieve in IMRT plans for NPC because of parapharyngeal extension of targets and because of the location of the deep lobe of the parotid.

Usually, the entire parotid is contoured as an organ at risk (OAR) in IMRT dose optimization for NPC patients. For the present study, we developed a superficial parotid lobe–sparing delineation approach in IMRT planning for NPC patients. In the control plans, we contoured both parotids in full as OARS in the traditional way, with a prescribed dose of 36 Gy. In the test plans, we contoured only the superficial parotid lobes as OARS, with a prescribed dose of 26 Gy. We then evaluated the dose changes to the parotid glands, the targets, and the other OARS.

## 2. METHODS

### 2.1 Patients

From August 2010 to January 2011, our study, conducted at the Nasopharyngeal Carcinoma Department of Sun Yat-sen University Cancer Center, enrolled 31 newly diagnosed patients with pathology-proven NPC. All patients had a World Health Organization performance status of 0–1 and received 9-field step-and-shoot IMRT. Table 1 shows the characteristics of the study patients.

### 2.2 Delineation of Superficial and Deep Lobes of Parotid Glands

In addition to each entire parotid gland, the superficial and deep lobes of the parotids were outlined on every computed tomography slice. The parotid gland is usually divided into a superficial lobe and a deep lobe by the posterior border of the mandible or the facial nerve that threads through it. The superficial lobe covers the front part of masseter muscle's posterior border anteriorly. Its trailing edge is adjacent to the front edge of mastoid and the anterior border of the upper side of the sternocleidomastoid muscle. The deep lobe is located in the retromandibular fossa and beneath the mandibular ramus<sup>13</sup>. For the present study, we drew the borders of the superficial and deep lobes of the parotids using the facial nerve process and anatomy (Figure 1).

### 2.3 IMRT Planning

All patients were immobilized with thermoplastic head–neck–shoulder masks in the supine position. Computed tomography slices for treatment planning (3-mm thickness) were made from the upper edge of the frontal sinuses to 2 cm below the clavicular head.

TABLE 1 Clinical characteristics of the nasopharyngeal carcinoma patients

Characteristic	Value [n (%)]
Patients	31
Sex	
Men	21 (67.8)
Women	10 (32.2)
Age (years)	
≤40	16 (51.6)
>40	15 (48.4)
T stage	
T1	7 (22.6)
T2	6 (19.4)
T3	13 (41.9)
T4	5 (16.1)
N stage	
N0	7 (22.6)
N1	8 (25.8)
N2	12 (38.7)
N3	4 (12.9)
Clinic stage <sup>a</sup>	
I	2 (6.5)
II	6 (19.4)
III	14 (45.1)
IV <sup>b</sup>	9 (29.0)
Histology	
WHO type I	0 (0)
WHO type II	0 (0)
WHO type III	31 (100)

<sup>a</sup> Union for International Cancer Control 2002 TNM staging system.

<sup>b</sup> Nonmetastatic patients only (stages IVA and IVB).

WHO = World Health Organization.

Contours for targets and OARS were delineated in a Monaco treatment planning system (version 3.0; Elekta, Stockholm, Sweden):

- The nasopharyngeal gross tumour volume (GTV<sub>nx</sub>) and cervical gross tumour volume (GTV<sub>nd</sub>) included the gross extent of the tumour found by physical examination and imaging studies.
- The clinical target volume 1 (CTV<sub>1</sub>) consisted of the high-risk region, including the GTV plus a 5- to 10-mm margin and the entire nasopharyngeal mucosa plus 5 mm into the submucosal area.
- The clinical target volume 2 (CTV<sub>2</sub>) consisted of potentially involved regions, including the CTV<sub>1</sub> plus a 5- to 10-mm margin and the high-risk lymphatic drainage area, which needs prophylactic irradiation.
- Planning target volumes (PTVs) were derived by expanding the CTVs by 3 mm three-dimensionally so as to preclude set-up variability.

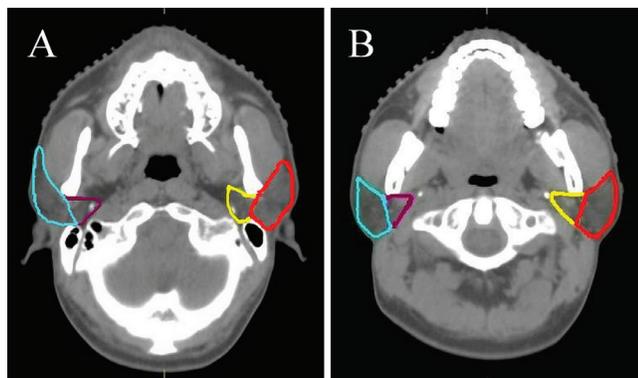


FIGURE 1 Delineation of the superficial and deep lobes of the parotid gland. (A) At the skull base, the boundary is the line from the stylomastoid foramen to the posterior border of the mandible. (B) When the stylomastoid foramen disappears, the boundary becomes the line from the anterior border of the sternocleidomastoid muscle to the anterior border of the mandible.

- The OARS included the spinal cord, brainstem, optic nerves, optic chiasm, parotid glands, lens, pituitary gland, temporal lobes, mid-ears, larynx, temporomandibular joints, and mandible.

All patients underwent IMRT in 30 fractions, 1 fraction daily, 5 days per week. A mono-isocentric technique was used for 9 coplanar and equally-divided fields with the isocentre set in the  $GTV_{nx}$ . The prescribed radiation dose was

- $PTV_{nx}$  (PTV of  $GTV_{nx}$ ): 68 Gy or 70 Gy for T1 patients, 70 Gy for T2–4 patients
- $GTV_{nd}$ : 64 Gy for positive lymph nodes
- $PTV_1$  (PTV of  $CTV_1$ ): 60 Gy
- $PTV_2$  (PTV of  $CTV_2$ ): 54 Gy

All targets were treated simultaneously. The prescribed doses to OARS other than the parotid glands were restricted according to the Radiation Therapy Oncology Group 0225 protocol<sup>14</sup>.

#### 2.4 Evaluation of Treatment Plan

For PTV homogeneity, the prescription dose encompassed at least 95% of the PTV. The  $PTV_{nx}$  volume receiving more than 110% of the prescription dose did not exceed 10%, and the  $PTV_{nx}$  volume receiving less than 93% of the prescription dose did not exceed 1%. The volume outside the PTVs receiving more than 110% of the prescribed dose to the  $PTV_{nx}$  did not exceed 1% or 1 cm<sup>3</sup>.

#### 2.5 Re-planning Using the Superficial Parotid Lobe–Sparing Delineation Approach

In the control IMRT plans,  $V_{36}$  (the percentage volume receiving 36 Gy or more) in the entire parotid was prescribed to be less than 40%. All treatment plans

were then re-planned according to the new superficial parotid lobe–sparing delineation requirement:  $V_{26}$  (the percentage volume receiving 26 Gy or more) in the superficial parotid lobe was prescribed to be less than 30%, without any change in the prescriptions for the targets and other OARS compared with the control IMRT plans. The same physicist created all the plans.

#### 2.6 Statistics

The Wilcoxon matched-pairs signed–rank sum test was applied to compare mean dose; percentage volume of target regions, the parotid glands, and other OARS receiving a specific dose; maximum dose in target regions; and homogeneity and conformity indices. All tests were two-sided. The level of significance was set at 5% ( $p < 0.05$ ). The statistical analysis was performed using the SPSS software application (version 16.0: SPSS, Chicago, IL, USA).

### 3. RESULTS

#### 3.1 Evaluation of Dose to the Parotid Glands

The mean volumes of the left and right parotid glands were 29.1 cm<sup>3</sup> and 28.7 cm<sup>3</sup> respectively. The mean volumes of deep lobes of the left and right parotid glands were 6.2 cm<sup>3</sup> and 6.0 cm<sup>3</sup> respectively. The deep lobes accounted for 21.3% and 20.9% of the entire left and right parotid glands respectively. Compared with the control plans, the study plans resulted in significantly lower mean doses to both entire parotid glands and in a significantly lower percentage volume receiving 30 Gy or more ( $p < 0.05$ , Table II). In the test plans, the mean dose to the left and right superficial parotid lobes decreased by 4.4 Gy and 4.0 Gy respectively. Depending on T stage, N stage, and clinical stage, the decrease in the dose to the superficial parotid lobes ranged from 2.3 Gy to 5.7 Gy (Table III).

#### 3.2 Evaluation of Dose to Targets

Dose distributions for targets were not significantly different between the control plans and the test plans ( $p > 0.05$ ); however, for patients staged T4, the volume of the PTV that received 110% of the prescription dose ( $V_{110}$ ) increased from a mean of 3.55% to a mean of 11.19% ( $p = 0.08$ ), with the measured  $V_{110}$  reaching 17.93% and 22.83% in two T4 patients (Figure 2). In the control plans, no patient had a  $V_{110}$  exceeding 10%.

To evaluate any differences in the homogeneity and conformity of the PTV, we compared the homogeneity and conformity indices between the control and test plans<sup>15</sup>:

$$\begin{aligned} \text{Homogeneity index}_{RTOG} &= MD / PD \\ \text{Conformity index}_{RTOG} &= V_{PD} / TV \end{aligned}$$

TABLE II Dose and change in dose to the parotids in the control and test plans

Variable	Dose		Change in dose (control – test)
	Control	Test	
<i>Dose to left parotid</i>			
Overall (Gy)			
Mean	38.5±5.5	34.9±5.0	3.6±4.8
Range	30.8 to 56.3	26.4 to 42.9	–3.9 to 22.5
Superficial lobe (Gy)			
Mean	33.5±5.1	29.1±4.0	4.4±5.1
Range	27.9 to 58.9	21.4 to 40.1	–4.4 to 24.4
V <sub>30</sub> (%)			
Mean	59.3±15.2	50.4±13.2	8.9±1.4
Range	37.5 to 100	22.4 to 78.1	–28.5 to 55.1
V <sub>60</sub> (%)			
Mean	11.4±9.0	9.9±8.4	1.0±5.0
Range	0.4 to 30.9	0.06 to 28.0	–8.38 to 14.4
<i>Dose to right parotid</i>			
Overall (Gy)			
Mean	38.5±5.6	34.5±5.2	3.5±4.3
Range	28.7 to 51.5	23.9 to 43.9	–2.7 to 18.6
Superficial lobe (Gy)			
Mean	33.7±5.0	29.7±4.2	4.0±4.8
Range	27.0 to 49.4	20.9 to 39.7	–3.7 to 18.6
V <sub>30</sub> (%)			
Mean	59.1±16.3	49.1±14.9	10.0±14.5
Range	34.0 to 100	16.1 to 74.5	–22.3 to 52.6
V <sub>60</sub> (%)			
Mean	9.3±7.8	8.3±8.3	1.0±5.0
Range	–0.1 to 30.4	0.0 to 31.8	–8.4 to 14.4

V<sub>30</sub> = percentage of the volume that received 30 Gy or more; V<sub>60</sub> = percentage of the volume that received 60 Gy or more.

where RTOG stands for “Radiation Therapy Oncology Group” and MD is the maximum dose, PD is the prescription dose, V<sub>PD</sub> is the volume receiving the prescription dose, and TV is the target volume.

No differences in the homogeneity and conformity indices were found between the control plans and the test plans ( $p > 0.05$ , Table IV).

### 3.3 Evaluation of Dose to Other OARs

Bilaterally, the dose to the lenses dropped slightly in the test plan. Doses to other OARs showed a small increase compared with doses in the control plans. In the test plans, the mean doses to the brainstem and spinal cord were 34.3 Gy and 28.7 Gy (increases of 1.4 Gy and 1.1 Gy respectively), the mean dose to the optic chiasm increased by 2.7 Gy to 41.0 Gy, the mean dose to the larynx increased by 1.4 Gy to 47.9 Gy, and the mean dose to the pituitary increased by 2.1 Gy to 52.1 Gy (Figure 3). For patients with T1–3

tumours, doses to all OARs remained within acceptable limits. However, for patients with T4 tumours, the mean V<sub>60</sub> (percentage volume receiving 60 Gy or more) for brainstem reached 3.2%. The mean doses to the optic chiasm, pituitary, bilateral middle ears, optic nerves, and larynx exceeded the lower limit of acceptability, but remained below the upper limit. Figure 4 shows the changes in the dose–volume histogram for 1 patient.

### 4. DISCUSSION

Xerostomia is a common radiation-related complication in NPC patients. Recently, IMRT has greatly eased that problem by delivering tumoricidal doses to target regions and by reducing the dose to the parotid glands at the same time. Most data about the relationship between radiation dose and parotid gland function has come from research into head-and-neck cancers. For some patients with head-and-neck cancer, only

TABLE III Change in dose to the superficial parotid lobes in patients with nasopharyngeal carcinoma at different T, N, and clinical stages, using superficial parotid lobe-sparing technology

Variable	Patients (n)	Superficial lobe	Dose in test plan (Gy)	Dose reduction (Gy)
<b>T stage</b>				
T1	7	Left	27.4	4.8
		Right	28.5	4.6
T2	6	Left	29.7	1.6
		Right	28.8	1.5
T3	13	Left	29.2	3.9
		Right	30.4	3.2
T4	5	Left	30.3	8.5
		Right	30.6	8.2
<b>N stage</b>				
N0	7	Left	29.2	3.8
		Right	31.2	3.6
N1	8	Left	30.4	2.4
		Right	29.5	2.3
N2	12	Left	28.6	5.7
		Right	29.5	5.6
N3	4	Left	27.5	5.4
		Right	28.3	3.1
<b>Clinical stage</b>				
I	2	Left	26.6	3.8
		Right	30.0	3.6
II	6	Left	30.7	2.4
		Right	29.6	2.3
III	14	Left	28.7	5.7
		Right	29.7	5.6
IVA-IVB	9	Left	29.0	5.4
		Right	29.6	3.2

the ipsilateral neck receives radiotherapy, and thus a low radiation dose to the contralateral parotid gland can be achieved.

Eisbruch *et al.*<sup>10</sup> proposed that, given unstimulated and stimulated saliva flow rates respectively recovered to 76% and 114% of pre-radiotherapy values at 12 months as a criterion, a mean dose of less than 26 Gy to one entire parotid gland is the threshold dose. Patients whose parotid glands received more than 26 Gy experienced low unstimulated and stimulated saliva flow rates that could not recover over time. Blanco *et al.*<sup>16</sup> also reported that, in conventional fractionation, a mean dose less than 25.8 Gy to one entire parotid gland could significantly lower the incidence of xerostomia; otherwise, saliva flow would be reduced to less than 25% of its pretreatment value. Münter *et al.*<sup>17</sup> also

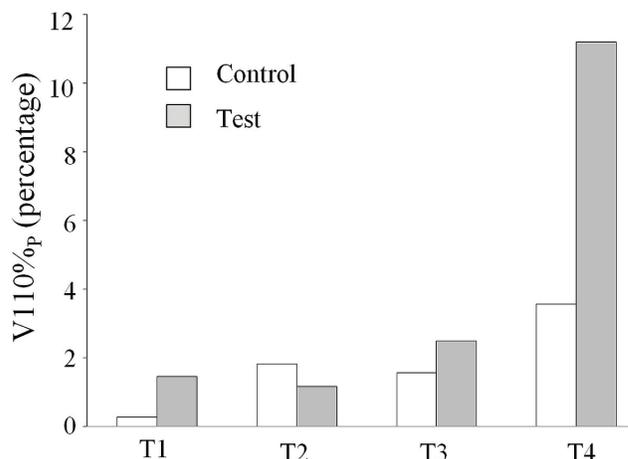


FIGURE 2 In the control and test plans for patients at various T stages, the planning target volume received 110% or more of the prescription dose ( $V_{110}$ ). Except in test plans for patients with T4 disease, the mean  $V_{110}$  was always less than 10%.

reported that a mean dose of less than 26–30 Gy to the entire parotid could significantly preserve salivary gland function.

However, the foregoing criteria are difficult to meet in NPC patients. Because of the special anatomic location and lymphatic drainage of the nasopharynx, both sides of the parapharynx and neck have to be included in radiation targets. As a result, the mean dose to the parotid usually exceeds 35 Gy. In 33 early-stage NPC patients treated with IMRT, Kwong *et al.*<sup>18</sup> reported that the mean dose to the parotid gland was 38.8 Gy. In their study of 139 NPC patients treated with IMRT, Zhao *et al.*<sup>12</sup> reported that the mean doses to the left and right parotid glands were 36.47 Gy and 36.72 Gy respectively. One year after radiotherapy, grades 0, 1, and 2 xerostomia were 10.6%, 64.9%, and 24.5% respectively. It is therefore urgent to lower the dose to the parotids in NPC patients treated with IMRT.

As already mentioned, the parotids as a whole are usually contoured as OARS in dose optimization for IMRT in NPC patients. However, overlap of the targets and the deep lobes of the parotids make dose optimization with protection of the parotids difficult. In 20 NPC patients with T3–4 disease, Chau *et al.*<sup>19</sup> reported changes in their OAR contouring of the parotid glands, splitting the organs into target-overlapping and non-target-overlapping subsegments. As a result, the mean dose to the parotids was reduced from 42 Gy to 38.6 Gy. At the same time, a significant improvement in target coverage and tumour control probability was able to be achieved.

In radiotherapy, the parotid can be considered a parallel organ. A  $V_{40}$  (percentage volume receiving 40 Gy or more) in the contralateral parotid gland of less than 33% has been reported to be satisfactory for complete salivary recovery after 24 months<sup>20</sup>, which suggests that if just part of the parotid were to

TABLE IV Dose changes in target regions, using superficial parotid lobe-sparing technology

Variable	Plan		p Value	
	Control	Test		
PTV <sub>nx</sub> V <sub>110</sub> (%)	Mean	1.65±2.61	3.39±5.33	0.10
	Range	0.00 to 8.78	0.00 to 22.83	
PTV <sub>nx</sub> V <sub>100</sub> (%)	Mean	99.62±0.66	99.73±0.57	0.06
	Range	97.80 to 100.00	97.89 to 100.00	
PTV <sub>nx</sub> V <sub>95</sub> (%)	Mean	99.94±0.19	99.92±0.29	0.58
	Range	99.21 to 100.00	99.10 to 100.00	
V <sub>60</sub> (%)	Mean	99.91±0.20	99.86±0.39	0.64
	Range	99.08 to 100.00	97.97 to 100.00	
V <sub>54</sub> (%)	Mean	99.40±0.55	99.32±0.47	0.30
	Range	97.88 to 99.97	98.34 to 99.95	
D <sub>max</sub>	Mean	77.95±1.88	78.84±2.56	0.07
	Range	74.24 to 85.52	74.39 to 85.17	
D <sub>mean</sub> to PTV <sub>nx</sub>	Mean	73.19±0.94	73.83±2.02	0.04
	Range	70.87 to 74.81	71.32 to 78.25	
D <sub>mean</sub> to PTV <sub>1</sub>	Mean	69.77±1.57	70.15±1.67	0.01
	Range	65.48 to 72.72	64.80 to 72.73	
D <sub>mean</sub> to PTV <sub>2</sub>	Mean	62.10±1.05	63.06±1.74	0.03
	Range	59.80 to 64.91	60.15 to 69.90	
Homogeneity index	Mean	1.12±0.02	1.13±0.03	0.07
	Range	1.09 to 1.18	1.09 to 1.22	
Conformity index	Mean	1.00±0.01	1.00±0.01	0.06
	Range	0.98 to 1.00	0.98 to 1.00	

PTV<sub>nx</sub>, PTV<sub>1</sub>, PTV<sub>2</sub> = planning target volume for the tumour, for the high-risk region, and for the potentially involved region; V<sub>110</sub>, V<sub>100</sub>, V<sub>95</sub> = volume covered by more than 110%, 100%, or 95% of the prescribed dose; V<sub>60</sub>, V<sub>54</sub> = percentage of the volume receiving 60 Gy or more, or 54 Gy or more; D<sub>max</sub> = maximum dose in target regions; D<sub>mean</sub> = mean dose.

be sufficiently protected, function could still be well preserved. The parotid gland is usually divided into superficial and deep lobes by the posterior border of the mandible and the facial nerve that threads through it. In the present study, we found that the superficial lobe of the parotid gland accounted for about 80% of the volume of the parotid gland as a whole, suggesting that a mean dose to the superficial parotid lobe

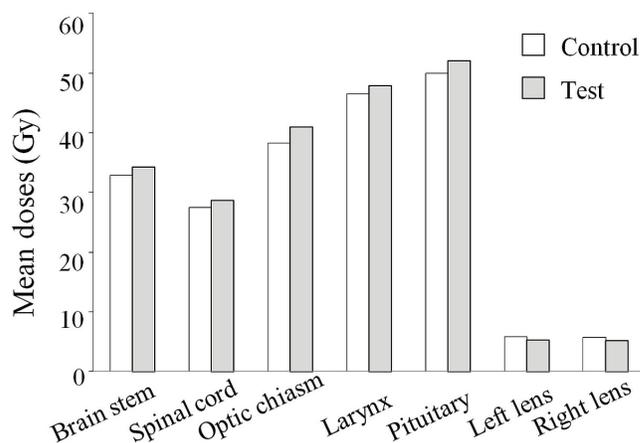


FIGURE 3 Changes in the dose to brainstem, spinal cord, optic chiasm, larynx, pituitary gland, and lenses between the control and test plans. Except for the lenses bilaterally, the mean dose to organs at risk increased slightly from the control to the test plans.

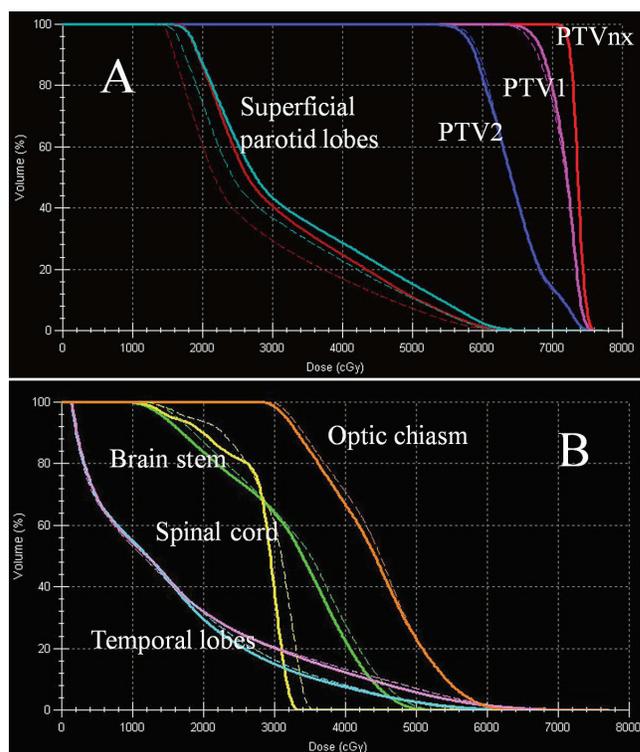


FIGURE 4 Dose–volume histogram for changes in target and organs at risk for a patient with T3N1M0 nasopharyngeal carcinoma. Dotted lines represent test plans, solid lines represent control plans. (A) The mean doses to the left and right superficial parotid lobes decreased significantly, with no significant change in target regions. PTV = planning target volume. (B) Doses to some organs at risk, such as the brainstem and spinal cord, showed small increases, but were within the prescription.

of less than 26–30 Gy would preserve its function substantially.

In the test IMRT plans, we used the superficial parotid lobes as the parotid OARS during dose optimization.

The results showed that, compared with the dose in the traditional plans, the mean dose to both entire parotid glands in the test plans declined by more than 4 Gy. Most importantly, the mean dose to the superficial parotid lobes in the test plans was 30 Gy or less regardless of clinical stage, and the  $V_{40}$  for the left and right parotids was 31.9% and 29.2% respectively. At the same time, we found that the dose distributions for the targets in T1–3 NPC patients were not significantly different between the control plans and the test plans. The homogeneity and conformity indices also were not different between the control plans and the test plans. Hence, contouring the superficial lobes of the parotids as the parotid OARS is feasible in IMRT planning for T1–3 NPC patients. However, in the test plans for T4 patients, we found that the percentage of the PTV receiving more than 110% of the prescription dose increased from 3.55% to 11.19% and that the mean  $V_{60}$  for the brain stem reached 3.2%. Those findings suggest that IMRT plans that try to overprotect the parotids might be not suitable for NPC patients with large local disease. In that situation, target coverage, rather than parotid protection, should be the first consideration.

## 5. CONCLUSIONS

A superficial parotid lobe-sparing delineation approach can significantly lower the mean dose to both entire parotid glands and to the superficial parotid lobes in T1–3 NPC patients. This approach would be expected to result in less xerostomia and better quality of life for the patients so treated.

## 6. CONFLICT OF INTEREST DISCLOSURES

The authors declare that they have no competing interests.

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