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ORIGINAL ARTICLE

Selective partial salivary glands sparing during intensity-modulated radiation therapy for nasopharyngeal carcinoma*

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Abstract

Objective This study evaluated the dosimetric consequences of selective partial salivary gland sparing during intensity-modulated radiotherapy (IMRT) for patients with nasopharyngeal carcinoma (NPC).

Methods Ten patients with NPC were enrolled in the study. Two IMRT plans were produced for each patient: conventional (control) and partial salivary glands-sparing (treatment), with dose constraints to the entire parotid glands or partial salivary glands (including the parotid and submandibular glands, delineated with the adjacent distance of at least 0.5 cm between the glands and PTV, the planning target volume) in planning, respectively. Dosimetric parameters were compared between the two plans, including the $V_{110\%}$, $V_{100\%}$, $V_{95\%}$ (the volume covered by more than 110%, 100%, or 95% of the prescribed dose), D_{min} (the minimum dose) of PTV, homogeneity index (HI), conformity index (CI), and the mean dose and percentage of the volume receiving 30 Gy or more (V_{30}) for the parotid glands and submandibular glands.

Results Treatment plans had significantly lower mean doses and V30 to both the entire parotid glands and partial parotid glands than those in control plans. The mean doses to the partial submandibular glands were also significantly lower in treatment plans than in control plans. The PTV coverage was comparable between the two plans, as indicated by $V_{100\%}$, $V_{95\%}$, D_{min}, CI, and HI. The doses to critical structures, including brainstem and spinal cord, were slightly but not significantly higher in treatment plans than in control plans.

Conclusion A selective partial salivary gland-sparing approach reduces the doses to parotid and submandibular glands during IMRT, which may decrease the risk of post-radiation xerostomia while not compromising target dose coverage in patients with NPC.

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Key words: nasopharyngeal carcinoma; intensity-modulated radiotherapy; selective partial salivary gland sparing

Radiotherapy is one of the main treatments for head and neck cancers, especially nasopharyngeal cancer. During radiotherapy, the salivary glands, parts of which are commonly included in or very close to the target volume, receive a high radiation dose on both sides, which can lead to xerostomia (dry mouth). Xerostomia can produce a number of negative effects on the patient's quality of life, affecting dietary habits, speech, taste, and increasing the risk of oral infections [1]. Intensity-modulated radiotherapy (IMRT) has now become the standard modality of radiotherapy for nasopharyngeal cancer, which may reduce xerostomia by delivering tumoricidal doses to the target volume while sparing normal structures at the same time; however, severe xerostomia is still experienced by many patients (39.3%) after IMRT [2].

Currently, the management of irradiation-induced xerostomia remains largely limited to palliative therapy. Sparing damage to the salivary glands during radiotherapy may be the key to preventing radiation-induced xerostomia. The salivary glands include three pairs of major salivary glands: the parotid,

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submandibular, and sublingual glands, as well as numerous minor salivary glands scattered throughout the oral cavity. The parotid gland mainly secretes saliva in stimulated conditions, contributing up to 60% of the total saliva, while the submandibular gland mainly secretes saliva in non-stimulated conditions, producing up to 90% of total saliva under non-stimulated conditions, but only 20%–40% of total saliva in stimulated conditions, while the sublingual gland produce 2%–5% of the total saliva upon stimulation [3]. Both the parotid and the submandibular glands have been shown to be sensitive to radiotherapy (TD_{50}, the former equal to 40 Gy and the latter 39 Gy) [4–5], and the mean doses, which represent the threshold for significant salivary flow reduction, are 26 to 39 Gy [6]. Conventionally, the entire parotid glands are contoured as critical structures, and due to parts of the glands being very close to or overlapping with the target volume, the mean dose limitation of less than 26 Gy is hard to achieve in IMRT plans.

In the present study, we developed a selective partial salivary gland-sparing approach during IMRT for nasopharyngeal cancer, which was delineated with the adjacent distance of at least 0.5 cm between the glands and the planning target volume (PTV), and evaluated the dose changes in the salivary glands, target volume, and critical structures.

Materials and methods

Patients

From May 2015 to May 2016, 10 patients with histologically proven nasopharyngeal carcinoma treated at Renmin Hospital of Wuhan University were included in this study. All patients had good performance status (WHO 0–1) and received 9-field step-and-shoot IMRT. An informed consent for radiotherapy was signed. Patient characteristics are described in Table 1. The regimen for concurrent chemoradiotherapy was cisplatin 70 mg/m^2 every 3 weeks for 1 to 2 cycles.

Pretreatment evaluation of tumor extent

A thorough pretreatment evaluation of tumor extent was performed for all patients, including a complete history and physical examination, mirror and fiberoptic examination, computerized tomography (CT) with contrast and magnetic resonance imaging (MRI) of the primary site and neck, chest X-ray, and liver sonography. Nasopharyngeal carcinoma was staged in accordance with the Chinese 2008 staging system [7].

CT simulation and delineation of target volumes and critical structures

Patients were immobilized in a supine and hard palate vertical position with a head support and a custom thermoplastic cast from head to shoulders. A high-resolution planning CT scan (General Electric Medical Systems, USA) was taken with contiguous 5-mm thick slices from the skull vertex down to below the clavicles with the cast on and in the treatment position. The CT images were transferred to a virtual simulation workstation computer for structure delineation. The target volumes and critical structures were contoured on the axial CT slices.

The gross tumor volume (GTV) represented the visible primary tumor and/or enlarged or suspicious lymph nodes identified either clinically or radiographically with MRI and CT. The clinical target volume (CTV) encompassed GTV plus a microscopic disease margin (at least 1.0 cm, except in areas adjacent to critical structures, i.e., brainstem). CTV_1 covered CTV and high-risk lymphatic areas, and CTV_2 covered lower-risk lymphatic regions. The planning target volume (PTV), PTV_{nx}, PTV_1, and PTV_2, were defined as the CTV (or CTV_1, CTV_2) plus 2 to 5-mm margins (depending on proximity to critical normal structures) to account for patient setup error.

Critical structures were also contoured on axial CT slices throughout the volume of interest, including the spinal cord, brainstem, eyes, lenses, optic nerves, optic chiasm, pituitary, temporal lobes, parotid glands, temporomandibular joints, and mandible.

Table 1 Patient characteristics

Patient	Age (years)	Gender	TNM staging	Concurrent chemotherapy
1	60	Male	$T_4N_1M_0$	No
2	48	Male	$T_4N_3M_0$	Yes
3	52	Male	$T_2N_2M_0$	Yes
4	29	Male	$T_4N_2M_0$	Yes
5	41	Male	$T_3N_1M_0$	Yes
6	50	Male	$T_2N_2M_0$	Yes
7	42	Female	$T_1N_2M_0$	Yes
8	50	Male	$T_2N_2M_0$	Yes
9	47	Female	$T_2N_2M_0$	Yes
10	62	Male	$T_2N_1M_0$	Yes

Delineation of partial salivary glands

Salivary glands include major glands (parotid, submandibular, and sublingual glands) and minor glands (located throughout the oral cavity within the submucosa). According to the target volumes (PTV), partial salivary glands to be spared were delineated with the adjacent distance of at least 0.5 cm between the glands and PTV. Sublingual and minor salivary glands were together regarded as a critical structure "mouth cavity and floor." Fig. 1 illustrates the delineation of partial salivary glands

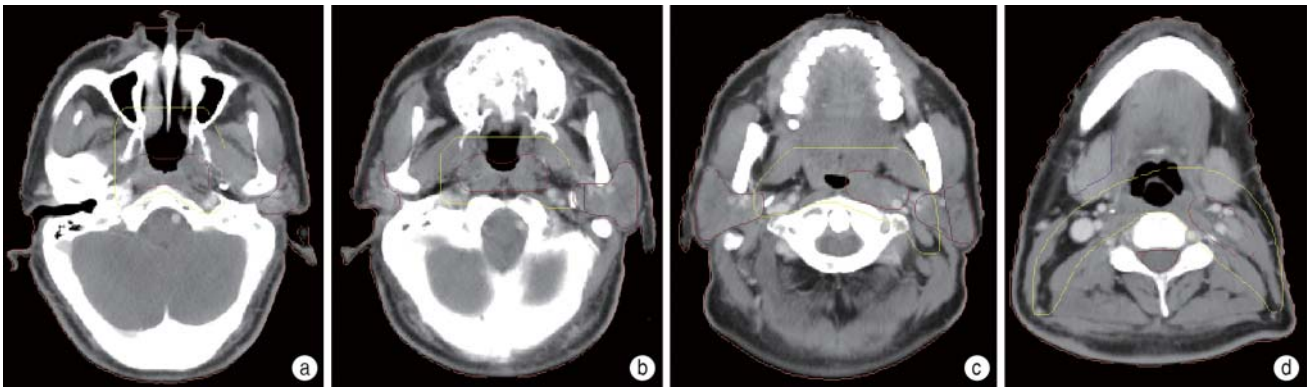

Fig. 1 Delineation of partial parotid and submandibular glands in a patient with $T_2N_2M_0$ nasopharyngeal carcinoma. GTV, PTV, entire parotid glands, partial parotid or submandibular glands are shown from the middle to the lateral in each CT image. (a) The left partial parotid gland is overlapped with the left parotid gland; (b) The right partial parotid gland is overlapped with the right parotid gland; but the left partial parotid gland is partly overlapped with the left parotid gland; (c) The right and left partial parotid glands are partly overlapped with the right and left parotid glands, respectively; (d) The right partial submandibular gland is delineated, but not the left partial submandibular gland due to too small volume left away from the PTV

in a patient with $T_2N_2M_0$ nasopharyngeal carcinoma.

Treatment planning

All patients underwent IMRT in 35 fractions, 1 fraction daily, 5 days per week. The following are the prescribed doses: PTV_{nx} (PTV of CTV), 70 Gy; PTV_1 (PTV of CTV_1), 60 Gy; PTV_2 (PTV of CTV_2), 50 Gy. The prescription dose is the isodose that encompasses at least 95% of the PTVs. No more than 20% of any PTV will receive 110% of its prescribed dose, no more than 3% of any PTV will receive < 93% of its prescribed dose, and no more than 1% or 1 cubic centimeter of the tissue outside the PTVs will receive > 110% of the dose prescribed to the PTV.

The dose constraints to critical structures were brainstem/pituitary maximum dose 54 Gy, spinal cord maximum dose 45 Gy, optic nerve/chiasm maximum dose 54 Gy, temporal lobes maximum dose 60 Gy, temporomandibular joints maximum dose 50 Gy, mandible maximum dose 60 Gy, eyes mean dose 35 Gy, and lens maximum dose 9 Gy.

Two IMRT plans were created for each patient: conventional (control) and partial salivary gland-sparing (treatment) IMRT. In the treatment IMRT plans, partial salivary glands, including parotid and submandibular glands, were defined as organs at risk (OAR) and incorporated into the IMRT optimization process; but in the control IMRT plans, the entire parotid glands were instead defined as OAR, and submandibular glands were not considered as OAR. The dose constraints for the entire parotid glands were V_{30} (percentage of the volume receiving 30 Gy or more) ≤ 50%; due to a smaller volume as compared with the entire glands and the threshold dose for the recovery potential of the glands, the dose constraints for partial parotid glands were V_{26} ≤ 30%. The dose constraints for the partial submandibular glands were V_{35} ≤ 50%. All the plans were created by the same physicist.

Dosimetric comparisons

For PTV, the volume covered by more than 110%, 100%, or 95% of the prescribed dose ($V_{110\%}$, $V_{100\%}$, $V_{95\%}$), and the D_{min} (the minimum dose) were compared between the control and treatment IMRT plans. The differences in the homogeneity and conformity of PTV were evaluated between the two plans. The homogeneity index (HI) was calculated with $HI = (D_{max} - D_{min})/D_{mean}$, where D_{max} is the maximum dose, D_{min} the minimum dose, and D_{mean} the mean dose within the target volume [8]. The lower the value of HI is, the better the homogeneity will be. The conformity index (CI) of PTV was defined as the ratio between the volume covered by the prescribed dose (V_{PD}) and the volume of the PTV (V_{PTV}): $CI = V_{PD}/V_{PTV}$. The value of CI ranges from 0 to 1, and the closer to 1, the better [9].

For OAR, the mean dose and V_{30} for parotid glands, the mean dose for submandibular glands, and the maximum dose (D_{max}) to the spinal cord, brainstem, and pituitary were also compared.

Statistical analysis

Data were analyzed using SPSS 14.0 software, and a Wilcoxon matched-pairs test was used. A probability value of ≤ 0.05 was considered significant.

Results

Evaluation of dose to salivary glands

Compared with control plans, treatment plans had significantly lower mean doses and V_{30} to both the entire

parotid glands and partial parotid glands ($P < 0.05$; Table 2). The mean doses to the partial submandibular glands were also significantly lower in the treatment plans than in the control plans ($P < 0.05$).

Evaluation of dose to targets and critical structures

As shown in Table 3, the $V_{100\%}$, $V_{95\%}$, and the D_{min} for the PTV (PTV_{nx} or PTV_1) were comparable between the control and treatment plans. Furthermore, there was no significant difference in the HI and CI of the PTV between the two plans. For the hot spot, the $V_{110\%}$ of the PTV_{nx} in the treatment plans was slightly higher but not significantly than that in the control plans ($P > 0.05$).

The doses to critical structures, including the brainstem and spinal cord, were slightly but not significantly increased in treatment plans as compared with control plans ($P > 0.05$).

Discussion

The parotid and submandibular glands produce up to 90% of total saliva under stimulated or non-stimulated conditions; therefore, they are the main salivary glands to be spared to prevent xerostomia after radiotherapy. Studies have shown that a mean dose of less than 26–39 Gy to the parotid or submandibular gland can preserve their function substantially after radiotherapy [6]. The parotid and submandibular glands are parallel organs. The volume of the contralateral parotid gland receiving > 40 Gy (V_{40}) being less than 33% has been reported to be satisfactory for complete salivary recovery at 24 months after IMRT [10]. Furthermore, the influence of the mean doses to the contralateral submandibular and parotid glands upon the recovery of saliva output has been shown to be equivalent to that of the mean V_{30} to the glands [11]. These facts suggest that if parts of the glands are sufficiently protected from irradiation-induced damage, their function can still be well preserved and xerostomia may be prevented.

During IMRT planning, the entire parotid glands are conventionally contoured as critical structures. However, parts of these glands are very close to or even overlap with the target volume, which makes it difficult to protect the glands during dose optimization. As a result, the mean dose to the parotid glands usually exceeds 32 Gy [2]. In the present study, we developed a selective partial salivary gland-sparing approach in IMRT for nasopharyngeal cancer, which was delineated with an adjacent distance of at least 0.5 cm between the glands and the target volume. The entire parotid glands or partial salivary glands were incorporated into the IMRT optimization process in

Table 2 Doses to the salivary glands in two plans

Variable	Control plan	Treatment plan	*P*
Right parotid			
Mean (Gy)	37.9 ± 5.5	33.8 ± 5.4	0.01
Range	28.3–48.8	25.5–45.2	
V_{30} (%) mean	43.7 ± 10.5	33.9 ± 11.4	0.02
Range	33.8–58.5	26.1–41.2	
Partial right parotid			0.01
Mean (Gy)	33.1 ± 5.2	29.1 ± 5.1	
Range	23.5–43.4	19.2–39.4	
Left parotid			
Mean (Gy)	36.8 ± 4.3	33.2 ± 5.0	0.01
Range	27.9–48.5	24.2–43.8	
V_{30} (%) mean	44.1 ± 11.4	34.8 ± 10.6	0.02
Range	34.2–59.3	27.3–41.8	
Partial left parotid			
Mean (Gy)	33.1 ± 5.2	29.1 ± 5.1	0.01
Range	23.5–43.4	19.2–39.4	
Partial submandibular			
Mean (Gy)	45.6 ± 8.3	35.6 ± 7.5	< 0.01
Range	39.2–55.1	28.8–44.1	

Table 3 Dose changes in target volume and critical structures in two plans

Variable	Control plan	Treatment plan	*P*
PTV_{nx} V_{110} (%)			
Mean	2.4 ± 2.2	3.5 ± 4.5	0.09
Range	0.0–6.0	0.0–9.2	
PTV_{nx} V_{100} (%)			
Mean	98.5 ± 0.7	98.6 ± 0.6	0.20
Range	97.8–100.0	97.9–100.0	
PTV_{nx} V_{95} (%)			
Mean	99.9 ± 0.2	99.9 ± 0.2	0.20
Range	99.3–100.0	99.2–100.0	
PTV_1 D_{min}			
Mean	44.6 ± 8.5	46.5 ± 7.4	0.20
Range	36.6–57.1	38.8–58.2	
HI			
Mean	0.15 ± 0.05	0.16 ± 0.06	0.10
Range	0.10–0.22	0.11–0.23	
CI			
Mean	1.20 ± 0.07	1.18 ± 0.08	0.10
Range	1.14–1.28	1.11–1.26	
Brainstem D_{max}			
Mean (Gy)	42.8 ± 5.2	43.6 ± 5.3	0.09
Range	39.8–47.6	41.2–49.1	
Spinal cord D_{max}			
Mean (Gy)	36.5 ± 5.2	38.7 ± 5.5	0.08
Range	34.5–43.8	37.6–44.2	
Right lens D_{max}			
Mean (Gy)	2.4 ± 1.0	2.4 ± 1.1	0.10
Range	1.8–3.7	1.7–3.9	
Right lens D_{max}	2.3 ± 1.0	2.2 ± 1.2	0.10
Mean (Gy)			
Range	1.7–4.1	1.8–4.0	

the control or treatment plans. The results showed that treatment plans had significantly lower mean doses and V_{30} to both the entire parotid glands and partial parotid glands than those in control plans. However, the PTV coverage was comparable between the two plans, as indicated by $V_{100\%}$, $V_{95\%}$, D_{min}, CI, and HI. The doses to critical structures, including brainstem and spinal cord, were slightly but not significantly increased in treatment plans as compared with control plans. Zhang *et al* reported that the superficial parotid lobe (partial parotid gland)-sparing delineation approach can lower the mean dose and V_{30} to both the entire parotid and superficial parotid lobe in patients with nasopharyngeal cancer without affecting dose distributions for targets [12], which is consistent with our present study. However, superficial parotid lobe-sparing delineation may exclude some parotid glands of the deep lobe, which may be sufficiently far away from the target volume to be spared in IMRT.

Submandibular glands produce up to 90% of the unstimulated saliva, which contains mucins and influences the degree of sensation of mouth dryness. Therefore, maintenance of their normal function may be useful to reduce radiotherapy xerostomia. Surgical transfer of a submandibular gland to the submental space prevents xerostomia after radiation therapy for head and neck cancers [13–14]. However, the submandibular glands are very close to the level II nodes, which are the common site of nodal metastasis in patients with nasopharyngeal cancer, making their sparing technically demanding. The mean dose to the submandibular glands usually exceeds 39 Gy [15], which is the highest threshold dose to preserve their function after radiotherapy [5].

Conventionally, the submandibular glands are given no dose constraint in the IMRT plan. In the present study, a selective partial submandibular gland-sparing approach was developed, which was delineated with the adjacent distance of at least 0.5 cm between the glands and the target volume. The results showed that the mean dose to the partial submandibular glands was significantly lower in the treatment plans than in the control plans. Restricting the dose to the submandibular glands may affect the dose distribution to PTV around the gland area. However, as stated above, the PTV coverage was not compromised in the treatment plans as compared with the control plans in the current study. Submandibular gland sparing with IMRT has been reported to be feasible in selected patients with head and neck cancer [15–16], and have a low risk of cancer recurrence in the vicinity of the spared glands [17].

In the present study, several patients with advanced T-stage (T_3 or T_4) were included. As stated above, the dosimetric parameters for PTV and critical structures (e.g., brainstem, spinal cord) in treatment plans for these patients were comparable to those in control plans, although some parameters (e.g., $V_{110\%}$ of the PTV) were slightly higher but not significantly, suggesting that the selective partial salivary gland-sparing approach is suitable for these patients with advanced T-stage. However, a similar partial salivary gland-sparing (i.e., the superficial parotid lobe sparing) approach was reported to be only indicated for patients with T1-3 NPC, arguing that T4 patients had increased $V_{110\%}$ of the PTV and dose to brainstem [12]. The reason for this discrepancy may be due to the different delineation of the spared salivary glands. In our study, the delineation of the spared salivary glands was dependent upon PTV to have an adjacent distance of at least 0.5 cm between the glands and PTV. Therefore, enough distance between the spared salivary glands and PTV can be assured to protect the glands without compromising the doses to PTV or other critical structures.

However, in the superficial parotid lobe–sparing approach, locally advanced tumor may extend close to the spared glands, which may affect the doses to PTV or other critical structures. In fact, exclusion of sparing of the deep lobe of the parotid glands (i.e., sparing the superficial lobe only) was reported to improve the dose coverage of PTV (preventing dose decreases to the lymphatic region) in IMRT for head and neck cancers, and this approach did not rule out patients with advanced T-stage [18]. In addition, in a study of recovery of salivary function after IMRT with bilateral superficial lobe parotid sparing versus contralateral parotid-sparing, patients with locally advanced head and neck cancers were enrolled, and the results showed that bilateral superficial lobe parotid-sparing reduces the risk of developing high-grade subjective xerostomia [19].

In conclusion, a selective partial salivary gland-sparing approach reduces the doses to parotid and submandibular glands during IMRT, which may decrease the risk of post-radiation xerostomia, while not compromising target dose coverage in patients with NPC. The selective partial salivary gland-sparing approach also has the potential to be applied to other head and neck cancers to achieve salivary gland sparing during IMRT.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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