Geometric Changes in the Parotid, Submandibular, and Thyroid Glands during Intensity Modulated Radiotherapy for Nasopharyngeal Carcinoma: A Cohort Study

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Abstract: *Background*: Intensity-modulated radiotherapy (IMRT) for nasopharyngeal carcinoma (NPC) acts on the tumor and affects surrounding organs at risk (OARs). This study aimed to quantify the geometric changes in the parotid gland, the submandibular gland (SMG), and the thyroid, during the course of treatment.

Methods: Twenty patients diagnosed with locally advanced NPC were consecutively enrolled, and received definitive chemoradiotherapy in 33 fractions over 6.5 weeks. Each patient underwent planning computed tomography (pCT) followed by six weekly repeat CTs (rCTs) without contrast enhancement. Each rCT was rigidly registered to its pCT. Changes in terms of volume, position, and shape of the OARs were assessed. Differences in left- and right-sided OARs were compared.

Results: Radiation doses to the parotid, SMG, and thyroid were 32.12 ± 11.2 Gy (mean ± standard deviation SD), 25.46 ± 8.62 Gy, and 18.89 ± 10.24 Gy, respectively. Volume reductions of 28.6% ± 14.6% (mean ± SD), 26.6% ± 17.1%, and 12.3% ± 11.3% were observed in the parotid, SMG, and thyroid, respectively. Rate of volume loss for the parotid and SMG decreased from 1.6-1.7% per day in the first week to 0.5%-0.6% in the last week. Contrarily, not all thyroid lobes decreased in volume during treatment. The center of mass of the parotid shifted 2.0-2.6 mm medially; for the SMG and thyroid, a 0.1-0.5 mm medial shift was noted. The displacement in the anterior-posterior and cranial-caudal directions was < 0.6 mm. The 3-dimensional vector displacements of the parotid and SMG were 2.2-2.9 mm, and that of thyroid was 4.0-4.3 mm. The overlapping metrics of all three OARs decreased over time, and the shortest perpendicular distance increased from 1.5-1.8 mm in the first week to 2.4-2.5 mm in the last week. The geometric differences between weeks were statistically significant (P<0.05).

Conclusions: The volume, position, and shape of the OARs changed significantly during IMRT for NPC. These geometric changes displayed a time association, suggesting the necessity to re-plan treatment for better sparing of these OARs.

Keywords: Intensity-modulated radiotherapy (IMRT), nasopharyngeal carcinoma (NPC), organ at risk (OAR), thyroid, submandibular gland, parotid gland, geometric changes, volume reduction.

BACKGROUND

Radiation therapy (RT) is the primary treatment modality for head and neck cancer [1]. Advanced RT techniques, such as intensity-modulated and/or imaging-guided RT [2], allow for targeted RT delivery to the tumor and selective sparing of healthy tissues, i.e., organs at risk (OARs) but also require high geometric accuracy [1, 3]. As methods to spare healthy organs are limited by lack of measurements of treatment induced changes, RT-related toxicities, especially to salivary and thyroid tissues, remain a serious concern [4]. Usually, RT is combined with chemotherapy over a 6- or 7-week period, during which substantial geometric changes can occur to the tumor itself and the surrounding OARs [5-11]. Previous studies have reported that the primary tumor and positive neck lymph node showed a 1.7-3.2% volume loss per treatment day, resulting in an overall volume reduction of 14.7-43% [5, 11, 12], while radiation doses changed substantially [6, 13]. Most OARs, especially the salivary glands, i.e., the parotid and the submandibular gland (SMG), undergo considerable volumetric and dosimetric changes [12, 13] in addition to significant positional displacement as a result of exposure to radiation [12]. Also, studies have reported substantial geometric changes in these exocrine glands sensitive to radiation, as a result of RT. Hence, a number of dose-volume parameters have been proposed as predictors of radiation-related xerostomia [14].

Thyroid, the largest endocrine gland, is also sensitive to RT; radiation-associated hypothyroidism may affect as many as 50% of patients, with the peak incidence occurring at one year after RT to the neck [15]. Thus, dose-volume parameters, e.g., the percentage of thyroid volume receiving radiation of 30 Gy or more (V30), could predict radiation-induced

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hypothyroidism [16, 17]. However, most of these dosimetric studies assumed no geometric variations in the OARs during the treatment course; thus, adaptation of treatment plans, to adjust for these observed deformations, was not part of the protocol [9, 18, 19]. Understanding RT-related geometric variations in the OARs might allow refinements in strategies aimed at sparing these OARs and potentially decrease overall RT-induced toxicities.

In this study, we present a multi-dimensional analysis of the geometric variations, including consecutive changes in the volume, position, and shape of the OARs, during the course of chemoradiotherapy for nasopharyngeal carcinoma (NPC).

METHODS

Patient Enrollment and Chemoradiotherapy

Twenty patients diagnosed with locally advanced NPC based on the American Joint Committee on Cancer (AJCC) head and neck cancer staging system (2010) were consecutively recruited at the Hubei Cancer Hospital from January 2011 to October 2012. The ethics committee of this hospital approved the study [6].

All patients provided written informed consent for participation in the study. Thirteen patients received concurrent and seven had sequential chemoradiotherapy; all chemotherapy regimens were platin-based: the dose of cisplatin was of 75mg/m^2 every three weeks or 40mg/m^2 each week with a maximum of seven weeks [6]. Each patient underwent a planning CT (pCT) scan with intravenous contrast before enrolling in a radiation plan that included six weekly repeated CT (rCT) scans (at the 5th, 10th, 15th, 20th, 25th, and 30th radiation fraction delivered) without contrast during a course of chemoradiotherapy. Images were then imported into software for geometric analysis [6, 7] of OAR delineation.

The chemoradiotherapy regimens, definitions of target volumes (TVs), OARs, and radiation planning were previously reported in detail [6, 7]. In brief, an inverse IMRT dynamic planning with nine equiangular coplanar beams was generated by a treatment planning software (Eclipse version 8.6, Varian Medical Systems, Palo Alto, CA, USA). The prescribed dose to the primary tumor and positive neck lymph nodes was 69.3–72.6 Gy, with a high-risk clinical target volume (CTV) of 59.4–62.7 Gy and an elective CTV of 54.0 Gy in 33 daily fractions. All treatments were delivered once daily, five days a week, on a Varian linear accelerator (Varian Medical Systems, Palo Alto, CA, USA). To document and assess the geometric changes in the OARs, the treatment plan for each patient was not modified during the treatment course.

Imaging Registration and Delineation of OARs

Each patient underwent one pCT and six rCT scans. Each rCT was rigidly registered to its pCT with bone matching based on our clinical protocol [6]. Upon registration, all seven CT images shared the same coordinate system for geometric analysis.

The OARs were delineated on both the left and right sides. Definitions of the glands were based on their anatomical structures. The parotid glands included the superficial and deep lobes and the left- and right-sided thyroid glands were divided arbitrarily along the midline of the human body. We defined the gland delineation in pCT as OAR1 and in rCT as OAR2. To minimize inconsistencies in the delineation, all OARs were contoured by the same radiation oncologist (W. Tan).

Metrics of Geometric Changes

The geometric changes in the OARs were assessed based on volume loss, positional displacement, and shape deformation. When comparing the same OAR in pCT and rCT, the volume in pCT (OAR1), rCT (OAR2), and the overlapping volume (OAR1∩OAR2) were automatically calculated. For each gland, parameters in pCT were baseline measurements and those in rCT were used to quantify any geometric changes. Volume reduction was calculated as $\frac{OAR1 - OAR2}{OAR1}$. The slopes of the relative change in volume over time for each OAR and each patient were calculated using linear regression analyses to estimate volume loss per treatment day [12].

The displacements of the center of mass (COM) were used to estimate the whole organ movement during treatment. Measurements of COM displacements included mean movement, system and random errors in the left-right (LR), anterior-posterior (AP), and cranial-caudal (CC) directions. The population group mean was defined as the average of the organ displacement in the population. Both system and random errors were calculated with the Van Herk method [20]. The 3-dimensional vector displacement (3D-Dis) was defined as the vector of the displacement distances in the LR, AP, and CC directions [6, 21], which can be used for evaluating volume displacement in space [22] and adequacy of margins [20].

Overlapping measures and surface-based distance analysis, as the shape estimation parameters [23], were used to evaluate contour variability [22]. For overlapping measures, the overlapping index (OI) and Dice similarity coefficient (DSC) were used to estimate the concordance between two OARs. The OI was calculated as $\frac{OAR1 \cap OAR2}{OAR1}$. and DSC as $\frac{2 \times (OAR1 \cap OAR2)}{OAR1 + OAR2}$. OI was used to estimate the ratio of OAR volume in rCT overlapped by that in pCT. Values of OI and DSC are both between 0 and 1 - the higher the value, the better the overlap [22, 24]. The OI and DSC might provide complementary information for estimating the OAR overlap during treatment.

Contour surface-based analysis could provide visualization of the areas of disagreement, and can be valuable in estimating inter-observer and multi-image contour variability [22, 23]. The shortest perpendicular distance (SPD) can be used to estimate the accuracy of delineation and contour variability [7, 25]. SPD was computed from two delineated surfaces, OAR1 and OAR2. With a point on each surface of OAR1 along its perpendicular direction, another closest point of OAR2 could be calculated automatically, and the distance between these two points was defined as SPD [7, 25]. As there are numerable points on the surface of OAR1, for each OAR in rCT, each point had a respective SPD. The mean and standard deviation (SD) of the SPDs were used to represent surface variability.

Statistical Analysis

One-way analysis of variance was used to compare volume, DSC, and mean SPD between weeks, and left- and right-sided OARs were compared using the Mann-Whitney U test. A two-tailed 5% significance level was considered statistically significant. The Statistical Package for Social Sciences (SPSS version 20.0; IBM Corporation, Armonk, NY, USA) was used for all analyses.

RESULTS

Fifteen patients were males and five females, with a median age of 45.5 years (range: 14-67 years). The radiation doses of the parotid, SMG, and thyroid were 32.12 ± 11.2 Gy (mean ± SD), 25.46 ± 8.62 Gy, and 18.89 ± 10.24 Gy, respectively. The median interval time between the pCT scanning and the first fractionation RT was 10 days (range 3-16 days). A detailed profile of the patients was previously described [6].

Volume Reduction

Compared with baseline measurements, the volume of the salivary glands, i.e., the parotid and SMG, decreased 10.2-11.7% in the first week and 38.9-40.6% in the last treatment week (Table **1**). Their volume change showed a similar time association (Figure **1**). The average volume reduction was 28.6% ± 14.6% (95% CI: 26.7%, 30.4%) for the parotid, and 26.6% ±17.1% (24.4%, 28.8%) for the SMG (Table **1**). There was no significant difference in any of the volume variations between the left- and right-sided glands. However, the rates of volume reduction differed between weeks and those differences were statistically significant. During the first three weeks of chemoradiotherapy, both salivary glands showed a trend for decreasing volume with increased RT fractions delivered, and had higher volume loss per treatment day than they did in the last three weeks. In the first three weeks, volume loss was 1.3-1.7% per treatment day, and in the last three weeks, 0.4-0.9% per day (Figure **2**).

For the thyroid gland, the volume reduced by 9.2% ± 8.9% (95% CI 6.4%, 12.1%) in the first week, and by 16.3% ± 14.3% (95%CI 11.7%, 20.8%) in the last

Table 1: Volume Reduction (in %) in the OARs during IMRT by Treatment Weeks

OAR	1st week	2nd week	3rd week	4th week	5th week	6th week	Mean	P value
Parotid	11.7±7.9 (9.1,14.2)	19.9±7.5 (17.5,22.4)	27.2±10.5 (23.9,30.6)	33.7±11.3 (30.0,37.3)	38.4±12.3 (34.5,42.3)	40.6±12.4 (36.6,44.5)	28.6±14.6 (26.7,30.4)	0.000
SMG	10.2±10.3 (6.9,13.5)	18.1±12.6 (14.1,22.1)	25.1±13.9 (20.6,29.5)	32.1±15.6 (27.1,37.1)	35.2±15.6 (30.2,43.7)	38.9±14.9 (34.1,43.7)	26.6±17.1 (24.4,28.8)	0.001
Thyroid	9.2±8.9 (6.4,12.1)	9.2±9.5 (6.1,12.2)	11.3±8.7 (8.5,14.0)	14.0±9.8 (10.9,17.1)	13.8±14.0 (9.3,18.3)	16.3±14.3 (11.7,20.8)	12.3±11.3 (10.9,13.7)	0.023

Note: Data are shown as mean ± standard deviation (95% confidence interval).
Abbreviations: IMRT intensity-modulated radiotherapy, OAR organ at risk, SMG submandibular gland.

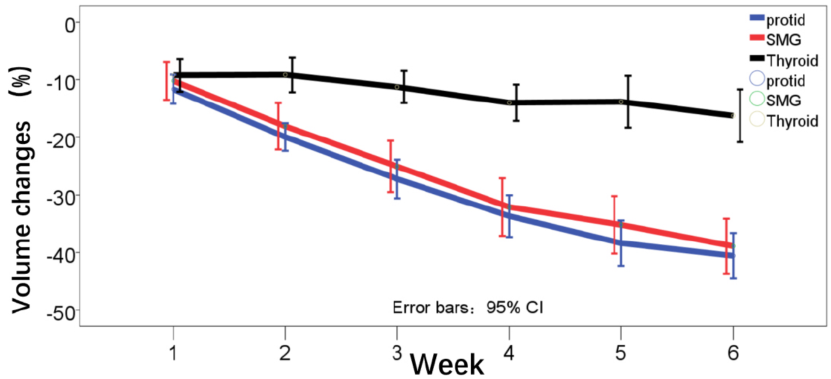

Figure 1: Weekly volume changes in the parotid, SMG, and thyroid during IMRT for NPC.

Abbreviations: SMG submandibular gland, IMRT intensity-modulated radiotherapy, NPC nasopharyngeal cancer, CI confidence interval.

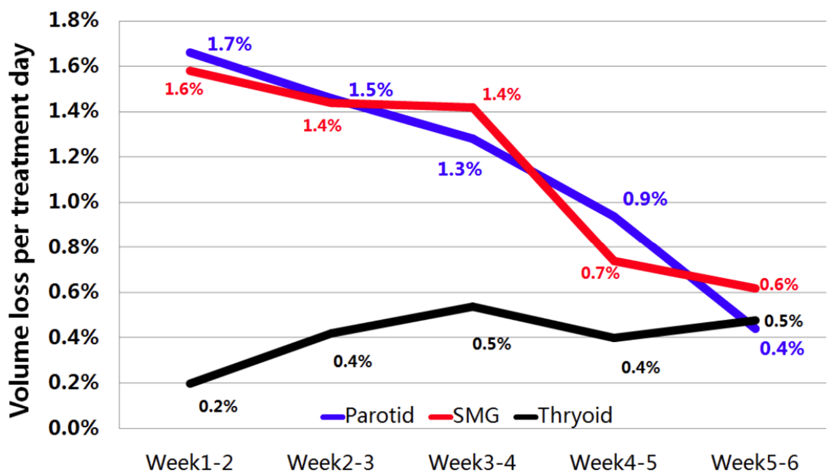

Figure 2: Volume loss in the parotid, SMG, and thyroid per treatment day during IMRT for NPC.

Abbreviations: SMG submandibular gland, IMRT intensity-modulated radiotherapy, NPC nasopharyngeal cancer.

week, with an average reduction of 12.3% ± 11.3% (95%CI 10.9%, 13.7%). In the first two weeks, the volume loss was 0.2% per treatment day, and did not change significantly afterwards (Figure **2**). However, six patients were found to have enlarged thyroid lobes; overall, 7.5-12.5% of the thyroid lobes increased in volume by 5.0-20.7% (Table **2**). Two patients presented with volume increases of more than 20% in the last two weeks.

Positional Displacement

The average position of the salivary glands moved by 0.1-2.6 mm, and of the thyroid by 0.1-0.5 mm. The parotid moved towards the midline of the body by 2.0-2.6 mm, and the SMG and thyroid by 0.1-0.4 mm and 0.1-0.3 mm, respectively (Table **3**). The COM of the salivary glands moved in the cranial direction by 0.5 mm, and that of the thyroid moved by 0.4-0.5 mm in the caudal direction. The parotid moved in the anterior

Table 2: Thyroid Volume Increase during IMRT by Treatment Weeks

	1st week	2nd week	3rd week	4th week	5th week	6th week
Patient numbers	4(20.0%)	5(25.0%)	3(15.0%)	2(10.0%)	3(15.0%)	3(15.0%)
Thyroid lobes *	4 (10.0%)	5(12.5%)	4 (10.0%)	4 (10.0%)	3 (7.5%)	3 (7.5%)
Volume increase (%)§	5.0± 1.4	9.6 ± 6.8	3.8 ± 4.2	3.5 ± 2.9	19.3 ± 18.0	20.7 ± 17.6

*For the left- and right-thyroid lobe, a total of 40 thyroid glands were included; the numbers in bracket indicate the percentage of thyroid glands with increased volume.
§Data are shown as mean ± standard deviation.

Table 3: Positional Displacements (mm) of the Parotid, SMG, and Thyroid

OAR	Direction	Mean	Systemic error	Random error	3D vector displacement
Parotid_L	LR	-2.6	0.5	1.3	2.9±1.1(1.5, 4.9)
	CC	0.5	0.8	1.1	
	AP	0.2	0.3	0.4	
Parotid_R	LR	2.0	0.5	1.4	2.9±1.0(1.7, 4.6)
	CC	0.5	0.3	0.6	
	AP	0.1	0.2	0.4	
SMG_L	LR	-0.4	0.4	0.6	2.2±1.1(1.2, 3.4)
	CC	0.6	0.3	0.8	
	AP	-0.5	0.3	0.6	
SMG_R	LR	0.1	0.3	0.5	2.3±1.4(0.6, 5.2)
	CC	0.5	0.4	0.8	
	AP	-0.3	0.4	0.6	
Thyroid_L	LR	-0.3	0.5	1.1	4.0±1.8(1.5, 7.3)
	CC	-0.5	0.8	1.8	
	AP	-0.5	0.6	1.2	
Thyroid _R	LR	0.1	0.5	1.2	4.3±1.9(2.0, 7.7)
	CC	-0.4	0.9	1.9	
	AP	-0.4	0.7	1.3	

Notes: Data are shown as mean ± standard deviation (95% confidence intervals). A negative number indicates a right, caudal, or posterior shift in the left-right (LR), cranial-caudal (CC), and anterior-posterior (AP) directions, respectively.
Abbreviation: SMG submandibular gland.

direction by 0.1-0.2 mm, while the SMG and thyroid moved in the posterior direction by 0.3-0.5 mm and 0.4-0.5 mm, respectively.

For the three OARs, system error was 0.3-0.5 mm in the LR direction, 0.3-0.9 mm in the CC direction, and 0.2-0.9 mm in the AP direction (Table **3**). Random error was 0.5-1.5 mm, 0.5-1.9 mm, and 0.5-1.3 mm in the LR, CC, and AP directions, respectively. The 3D-Dis of the salivary glands was 2.2-2.9 mm, and that of the thyroid was 4.0-4.3 mm.

Shape Variations

The OI and DSC decreased with increasing RT fractions (Table **4**). Though the OI stayed above 0.5 throughout treatment (Figure **3A**), the DSCs were lower than 0.75 after the second (for thyroid), third (for parotid), and fourth week (for SMG) (Figure **3B**), suggesting that glands delineated in rCT could not overlap well with those in their pCTs.

Surface deformation, evaluated by SPD, increased with time. The average SPDs of all these glands were 1.5-2.5 mm (Table **4**). The SPDs in the first week for the parotid, SMG, and thyroid were 1.5 mm, 1.5 mm, and 1.8 mm, respectively; and 2.4 mm, 2.5 mm, and 2.5 mm, respectively, in the sixth week. For all OARs, the SDs were slightly smaller than the corresponding mean SPDs, indicating that the glands underwent substantial surface changes.

The SPDs of the left- and right-sided SMG were significantly different ($P<0.001$), while measures of the other left-and-right organ pairs were not.

DISCUSSION

During treatment for NPC, subsequent changes may occur in the primary tumor and surrounding tissues/glands, which presents a challenge for effective sparing of healthy organs. Our results showed that the salivary and thyroid glands underwent substantial geometric changes during chemoradiotherapy for NPC, including the volume, position, and shape. Typically, the COM of the OARs is displaced asymmetrically. Our findings were consistent with this knowledge. Moreover, the concordance of shape measures became suboptimal and the discrepancies increased over time. This provides the ground for defining

Table 4: Consecutive Shape Change in the Parotid, SMG, and Thyroid during IMRT for NPC

Metrics	week	OI	DSC	SPD (mm)	SD of SPD (mm)
Parotid	1st	0.748±0.108 (0.714, 0.783)	0.852±0.064 (0.832, 0.872)	1.55±0.61 (1.36, 1.75)	1.07±0.41 (0.94, 1.20)
	2nd	0.749±0.092 (0.720, 0.778)	0.821±0.067 (0.800, 0.843)	1.83±0.58 (1.65, 2.01)	1.26±0.36 (1.15, 1.38)
	3rd	0.729±0.079 (0.704, 0.755)	0.794±0.095 (0.763, 0.824)	1.98 ±0.66 (1.76, 2.19)	1.40±0.49 (1.25, 1.56)
	4th	0.718±0.082 (0.692, 0.744)	0.748±0.102 (0.716, 0.781)	2.32±0. 91 (2.03, 2.61)	1.64±0.59 (1.46, 1.83)
	5th	0.710±0.089 (0.682, 0.739)	0.730±0.098 (0.706, 0.769)	2.31±0.70 (2.09, 2.54)	1.66±0.44 (1.52, 1.81)
	6th	0.690±0.100 (0.658, 0.722)	0.724±0.111 (0.689, 0.760)	2.35±0.57 (2.17, 2.54)	1.70±0.39 (1.57, 1.82)
	Mean	0.724±0.093 (0.712, 0.736)	0.780±0.101 (0.767, 0.792)	2.06±0.74 (1.96, 2.15)	1.46±0.50 (1.39, 1.52)
	P-value	0.000	0.000	0.000	0.000
SMG	1st	0.781±0.144 (0.735, 0.827)	0.869±0.102 (0.837, 0.902)	1.54±1.25 (1.14, 1.94)	1.02±0.97 (0.71, 1.33)
	2nd	0.703±0.159 (0.652, 0.754)	0.814±0.126 (0.774, 0.854)	1.93±1.42 (1.47, 2.40)	1.36±1.15 (0.99, 1.74)
	3rd	0.654±0.154 (0.604, 0.703)	0.779±0.128 (0.738, 0.820)	2.16±1.40 (1.71, 2.61)	1.59±1.20 (1.21, 1.98)
	4th	0.594±0.139 (0.550, 0.638)	0.735±0.123 (0.695, 0.774)	2.30 ±1.30 (1.89, 2.72)	1.80±1.12 (1.44, 2.16)
	5th	0.564±0.143 (0.518, 0.611)	0.710±0.130 (0.668, 0.752)	2.39±1.28 (1.97, 2.80)	1.93±1.10 (1.57, 2.29)
	6th	0.526±0.143 (0.480, 0.572)	0.677±0.130 (0.668, 0.752)	2.53±1.21 (2.15, 2.92)	2.11±1.13 (1.75, 2.47)
	Mean	0.637±0.170 (0.616, 0.659)	0.764±0.139 (0.746, 0.782)	2.14±1.34 (1.97, 2.32)	1.64±1.16 (1.49, 1.78)
	P-value	0.000	0.000	0.013	0.000*
Thyroid	1st	0.625±0.093 (0.596, 0.655)	0.765±0.076 (0.741, 0.790)	1.84 ±0.64 (1.63, 2.04)	1.43±0.54 (1.25, 1.60)
	2nd	0.577±0.140 (0.532, 0.621)	0.722±0.117 (0.684, 0.759)	2.27±1.00 (1.95, 2.59)	1.77±0.81 (1.51, 2.03)
	3rd	0.578±0.132 (0.535, 0.620)	0.724±0.108 (0.689, 0.758)	2.17±0.78 (1.92, 2.42)	1.70±0.67 (1.49, 1.91)
	4th	0.525±0.163 (0.473, 0.577)	0.673±0.151 (0.624, 0.721)	2.44±0.95 (2.13, 2.74)	2.02±0.94 (1.7.2, 2.32)
	5th	0.528±0.152 (0.479, 0.576)	0.677±0.148 (0.629, 0.724)	2.45±1.04 (2.12, 2.78)	1.98±0.96 (1.68, 2.29)
	6th	0.506±0.131 (0.464, 0.548)	0.662±0.119 (0.624, 0.700)	2.51±0.89 (2.23, 2.80)	2.05±0.83 (1.78, 2.31)
	Mean	0.556±0.142 (0.538, 0.574)	0.704±0.126 (0.688, 0.720)	2.28±0.91 (2.16, 2.40)	1.82±0.83 (1.72, 1.93)
	P-value	0.001	0.001	0.009	0.004

Data are shown as mean ± standard deviation (95% confidence interval).
Abbreviations: IMRT intensity-modulated radiotherapy, SMG submandibular gland, DSC Dice similarity coefficient, OI overlapping index, pCT planning computed tomography, rCT repeat computed tomography, SPD shortest perpendicular distance, SD standard deviation.

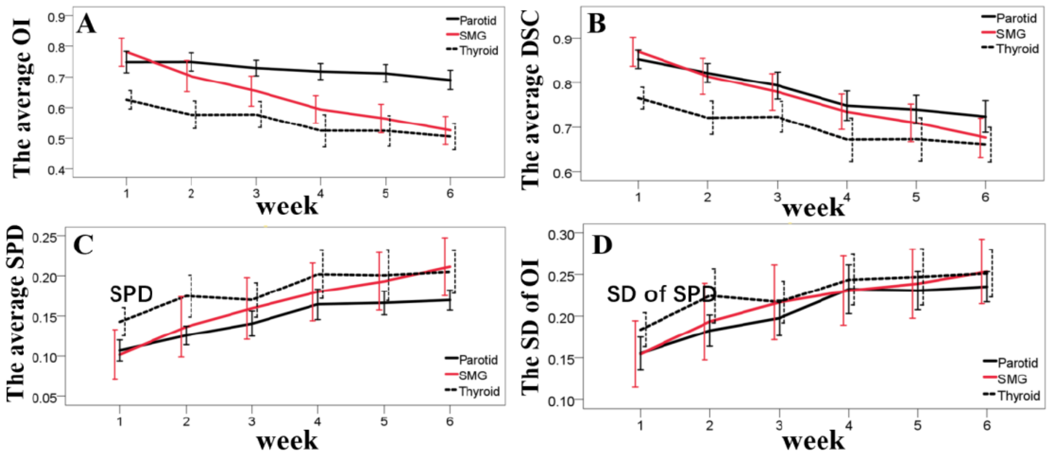

Figure 3: Contour comparisons for the parotid, SMG, and thyroid during IMRT: OI (**A**); DSC (**B**); SPD (**C**) and SD of SPD (**D**).

Abbreviations: OI: Overlapping index; DSC: Dice similarity coefficient, SPD: shortest perpendicular distance, SD: standard deviation.

intervals of treatment re-planning to optimize RT strategies for NPC and other head and neck cancer.

Geometric Changes in the Salivary Glands

Radiation-induced xerostomia occurs in 80% of head and neck cancer patients who receive RT [26]. Patients suffering from xerostomia have a hypofunction of the salivary output. Reducing radiation dose to the parotid and/or SMG appears to decrease the risk for xerostomia [14]. Yet, in the use of dose-volume metrics related to xerostomia, it is frequently assumed that no geometric changes occur over the treatment course [14].

Several studies have investigated the volumetric and dosimetric variations in the salivary glands during chemoradiotherapy in head and neck cancer [5, 12-14, 18, 27-33]. The absolute volume loss of the parotid was reportedly 0.20 cm^3 per treatment day [5] and 4.5-6.7% per week [29, 30]. The average volume reduction of the ipsilateral parotid was 14-31.9%, and that of the contralateral parotid 5-26.4% [12, 13, 18, 27, 28, 31]. In our study, the parotid showed a larger volume loss in the first half of the treatment course. Specifically, the overall volume reduction in the parotid was >40% when compared to the baseline, with a varied rate of loss in different treatment weeks. The parotid glands of both sides had a similar pattern of spatial displacement at comparable magnitude; and the concordance was less than acceptable after the third week.

The SMG, an important OAR that produces saliva, had a shrinking pattern similar to that of the parotid. Other studies have reported that the volume loss in the SMG was 1.3-1.5% per treatment day [12] and overall volume reduction of 11-30% [13, 28, 33]. Our results were consistent with previous findings, and we found an asymmetrical shift of the SMG in the medial-lateral direction. The shape change in the SMG was significantly different for the left and right SMG.

Geometric Changes in the Thyroid

Radiation-induced hypothyroidism (RIHT), a frequent late effect of RT, is a risk factor for vascular damage. Clinical RIHT was reported in 6-20% and subclinical/biochemical RIHT in 24-50% of head and neck cancer patients who received RT [17]. The potential risk factors of RIHT include small pre-treatment thyroid volumes, high mean thyroid dose[34], high dose per fraction [15], and V30 [16, 35].

The volume loss for the thyroid in our sample was not as substantial as that for the salivary glands, possibly due to the location of the glands and lower dose of radiation received. We furthered found that some patients experienced increased thyroid volume, as much as 20% over baseline, but whether these changes were clinically relevant was unclear. For the thyroid glands, the shape change increased over time, and the concordance of the shape measurements subsequent to treatment was below acceptable level after the second week.

Clinical Implications

Novel treatment techniques used in head and neck cancer, including IMRT and volumetric modulated arc therapy, have made the delivery of high dose gradients possible, although superb geometric accuracy is required. We found that OARs surrounding the tumor underwent significant volume and shape changes, as well as positional displacement during treatment. Moreover, considerable changes occurred in the first half of the treatment course, which may well affect the dose distribution if no modifications are made. This provides us the basis in finding measures to optimize dose delivery and planning reasonable margin to spare healthy tissues.

In head and neck cancer, high-risk neck nodal levels are usually included as elective TVs. Some of the neck nodal levels, such as levels I, II, IVa, and VIb, are delineated according to the anatomic surface of the parotid, SMG, and thyroid glands [36, 37]. For these special regional nodal levels, an additional 1-3 mm margin may be needed when defining the TV, considering the variations of these OARs. For head and neck cancer, our results indicated that the anisotropic PTV margin might be more reasonable in the re-planning, which take into account the geometrical changes of the tumor and/or OARs, anatomical sublocation, and the patient's weight loss, etc.

Strengths and Limitations

We presented a comprehensive profile of the geometric changes in important surrounding organs during the course of RT treatment for NPC. Also, to the best of our knowledge, this study was the first to report geometric changes in the thyroid in relation to RT for NPC. We found that, contrary to our expectation of RT-induced shrinkage of the OARs, some patients experienced enlarged thyroid lobes during the course of treatment.

The study had a few limitations. First, dosimetric measures are crucial in the development/validation of treatment modifications but were not included in the study. However, dosimetric outcomes highly depend on the accuracy of the OAR geometrics, which was the subject of our study. Second, one single match box was used for imaging registration, and multiple region registration could have improved the match results [38]. However, it is our standard of practice at the moment and it has acceptable global match performance. Lastly, subgroup analysis was not reasonable due to the small sample size, and we were not able to examine thoroughly characteristics of those with enlarged thyroid lobes subsequent to treatment. Future studies can examine groups with certain characteristics, to better understand subgroup-specific treatment response.

CONCLUSIONS

The volume reduction, positional displacement, and shape variation in the three OARs were substantial and quantifiable during chemoradiotherapy for NPC. The geometric variations observed suggested that adaptive re-planning is necessary for better organ sparing.

Our results can inform strategies for optimizing RT for NPC and reducing side effects. In particular, re-planning or adaptation needs to be completed by the third week (halfway of treatment) to better spare the OARs, if more frequent modifications are unrealistic. Further investigation on the dosimetric variations resulting from the geometric changes is needed to facilitate the design of adaptive solutions and/or personalized treatment plans. Future studies are also needed on research of re-setting the dose-volume parameters to TVs and OARs in the context of re-planning.

ABBREVIATIONS

RT = radiation therapy

IMRT = intensity-modulated radiotherapy

OAR = organ at risk

NPC = nasopharyngeal cancer

TV = target volume

CTV = clinical target volume

SMG = submandibular gland

rCTs = repeat computed tomography

pCT = planning computed tomography

RIHT = radiation-induced hypothyroidism

CI = confidence interval

SD = standard deviation

OI = overlapping index

DSC = Dice similarity coefficient

DECLARATIONS

Ethics Approval

The ethics committee of the Hubei Cancer Hospital approved this study.

Consent for Publication

All participants provided written informed consent for participation in this study and publication of results.

Availability of Data and Material

The datasets used in the study are available from the corresponding author upon reasonable request.

Competing Interests

None to declare.

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Authors' Contributions

WT and MY analyzed the imaging data, performed data analyses, and wrote the manuscript. WT and DH design the study, participated in data analysis and contributed to writing. WT , YD and DH organized the study and contribute to writing. All authors read and approved the final manuscript.

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