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ORIGINAL ARTICLE

A longitudinal evaluation of early anatomical changes of parotid gland in intensity modulated radiotherapy of nasopharyngeal carcinoma patients with parapharyngeal space involvement

Yingting Zhang, BSc,[1] Chengguang Lin, BSc,[1] Jianhua Wu, BSc,[1] Xiaobo Jiang, BSc,[1] Shara W. Y. Lee, PhD,[2] Shing-yau Tam, BSc,[2] & Vincent W. C. Wu, PhD[2]

[1]State Key Laboratory of Oncology in South China, Sun Yat-sen University Cancer Center, Guangzhou, China
[2]Department of Health Technology and Informatics, Hong Kong Polytechnic University, Hong Kong SAR, China

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Correspondence
Vincent W. C. Wu, Department of Health Technology and Informatics, Hong Kong Polytechnic University, Hong Kong SAR, China. Tel: +852 3400 8567;
Fax: +852 2362 4365;
E-mail: htvinwu@polyu.edu.hk

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Abstract

Introduction: Radiotherapy of nasopharyngeal carcinoma patients with parapharyngeal space (PPS) involvement may deliver high dose to the parotid gland. This study evaluated parotid gland changes during and up to 3 months after radiotherapy. **Methods:** Kilovoltage computed tomography (CT) scans of head and neck region of 39 nasopharyngeal carcinoma patients with PPS involvement were performed at pre-radiotherapy, 10th, 20th and 30th fractions and 3 months after treatment. The parotid glands were contoured in pre-radiotherapy planning CT scan and in subsequent scans. Dice similarity coefficient (DSC), percentage volume change and centroid movement between the planning CT and the subsequent CTs were obtained from the contouring software. In addition, the distance between medial and lateral borders of parotid glands from the mid-line at various time intervals were also measured. **Results:** The ipsilateral parotid gland received a mean dose of about 5 Gy higher than the contralateral side. The mean DSC and parotid volume decreased by more than 30% at 20th fraction and reached the minimum at 30th fraction. Partial recovery was observed at 3 months after treatment. The centroid displacement followed a similar pattern, which moved medially and superiorly by an average of 0.30 cm and 0.18 cm, respectively, at 30th fraction. The changes in ipsilateral gland were slightly greater than the contralateral side. **Conclusions:** Substantial volume change and medial movement of parotid gland were observed with slightly greater magnitude in the ipsilateral side. Adaptive radiotherapy was suggested at around 15th to 20th fraction so as to optimise the original dose distribution of the plan.

Background

The parapharyngeal space (PPS) is an inverted pyramidal fat-filled space lateral to the pharynx at the level of the first to third cervical vertebrae. Its lateral border is adjacent to the deep lobe of the parotid gland anterolaterally and the medial pterygoid muscle posterolaterally. As it is situated in close proximity to the posterolateral aspect of the nasopharynx, it is a common area of direct and lymphatic spread for primary nasopharyngeal carcinoma (NPC).[1] According to Sham et al.,[2] tumour extension outside the line joining the free edge of medial pterygoid plate posterior to lateral border of carotid artery is defined as PPS involvement. It has been reported that approximately 74–84% of the NPC patients presented with either unilateral or bilateral PPS involvement.[2,3]

The primary treatment modality for NPC is radiotherapy with a total dose of 66–76 Gy over a course of 6–7 weeks. Concurrent chemotherapy is used for moderate to advanced stage diseases. As NPC primary tumour and lymph nodes are relatively sensitive to radiotherapy and patients usually experience weight loss and alteration in muscle mass and fat distribution during a radiation course,[4] anatomical changes and shrinkages in organs are common in patients during the radiotherapy course.[5–9] This phenomenon is expected to be obvious in the ipsilateral parotid gland for patients with PPS involvement because the target is anatomically close to the parotid gland.

The parotid gland has been reported to migrate during a radiotherapy course.[8,10,11] If this happens, the gland may enter into the high-dose zone that is designed to cover the planning target volume (PTV). As a result, the parotid gland will receive a much higher than the planned dose.[12,13] Since the parotid gland accounts for 60–65% of total saliva production, high dose to this organ can further increase the risk of xerostomia.[14] In order to solve this problem, adaptive radiotherapy has been suggested in which the treatment plan is modified based on the tumour response and anatomical changes of OARs during a radiotherapy course.[13,15]

This study was unique as it evaluated the specific relationship between PPS involvement and anatomical changes of parotid glands during and just after the completion of external beam radiotherapy. The aims were to establish patterns of anatomical changes of parotid gland and propose an optimal time of replanning for these patients.

Methods

Thirty-nine adult NPC patients with unilateral PPS involvements treated with external beam radiotherapy and concurrent chemotherapy in Sun Yat-sen University Cancer Center (SYSUCC) between January 2011 and April 2013 were recruited. Ethics approval was obtained from the Cancer Hospital, Sun Yat-sen University. All patients were treated with intensity modulated radiotherapy (IMRT) using 6 MV photons with prescribed doses of 66–76 Gy to the target volume in 30–33 fractions. Computed tomography (CT) scans of the head and neck region in treatment position were conducted for the patients before radiotherapy treatment (planning CT), after 10th, 20th and 30th fractions during the radiotherapy course and 3 months after the completion of treatment. Informed consent was obtained from all patients before conducting the scans.

MIM Maestro (Version 6.3.4, MIM Software, Inc., Cleveland, OH, USA) was employed to contour the parotid glands in the CT scan images. Manual contouring was performed by the same dosimetrist on the planning CT followed by the deformable registration of parotid glands applied to the subsequent sets of CT. Manual adjustment was made after image registration to refine the contours. Rigid image registration of the pre-radiotherapy (pre-RT) parotid gland contour was applied to the CT taken at the subsequent time intervals, and they were compared with the deformed parotid contour to assess the anatomical deviations using the Dice similarity coefficient (DSC). DSC is a spatial overlap index for volumetric comparison and was defined by the following equation:

$$2|V_1 \cap V_t|/V_1 + V_t$$

where V_1 and V_t were volumes of parotid gland contoured at pre-RT and subsequent time intervals respectively.

The volume and centroid of parotid glands at each time interval were also measured by the MIM software. Since the high-dose volume was mainly located medially to the parotid glands, its migration in the transverse direction was studied. In order to assess the transverse displacement of the parotid glands, a horizontal line, which was perpendicular to the mid-line and just touching the anterior tip of odontoid process,[16] was drawn on the respective CT slice. This line made two intersections (medial and lateral) with each parotid gland (Fig. 1), and the distances between these two points with the mid-line[17] were measured and recorded at each time interval. These distances at each time interval were compared with the pre-RT dimensions so as to obtain the percentage changes. In addition, the change in patient

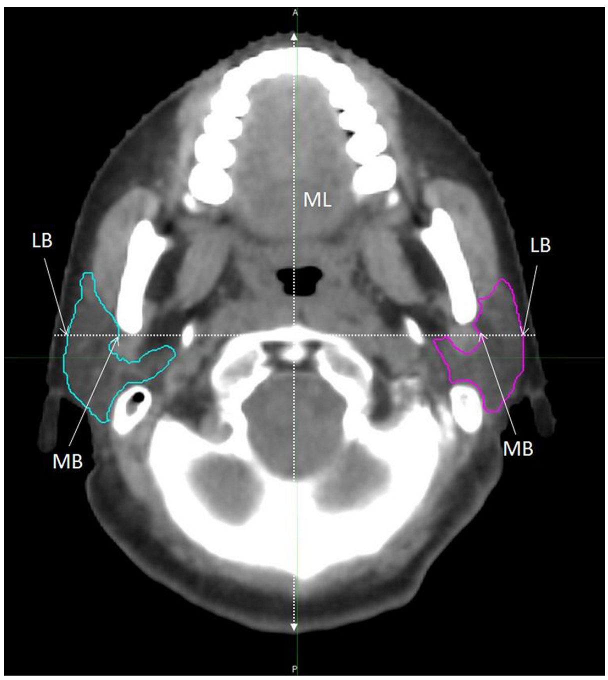

Figure 1. A transverse computed tomography slice at the level of odontoid process showing the parotid gland contours. The points of the lateral border (LB) and medial border (MB) are indicated and their distances from the mid-line (ML) are measured for analysis.

size was also monitored by measuring the anteroposterior (AP) and lateromedial (LM) separations in the same CT slice.

Paired *t*-test was used to evaluate the differences between the mean measurements of two consecutive time intervals. Independent *t*-test was used to evaluate the differences in the parameters between the ipsilateral and contralateral sides. Wilcoxon signed-rank test and Mann–Whitney test were used, respectively, if the data were not normally distributed. All statistical tests were performed using the Statistical Package for the Social Science (SPSS, IBM Corporation, New York, NY, USA) software version 22.0.

Results

The median age of the 39 NPC patients was 48 (range 29–76) and the gender ratio between male and female was 2.3:1. Nineteen (48.8%) and 20 (51.2%) patients presented with left and right PPS involvement respectively. The mean doses to the ipsilateral and contralateral parotid glands were 56.3 ± 6.2 Gy and 51.7 ± 9.2 Gy respectively. The mean LM separation of the patients decreased by 7.2% at 60 Gy and returned to −3.2% at 3 months after treatment, whereas the mean AP separation decreased by less than 1% throughout the study period. The mean DSC for ipsilateral parotid gland decreased to 0.63 at 30th fraction and returned to 0.74 at 3 months after treatment (Fig. 2). All differences between each pair of consecutive measurements (such as between 10th and 20th fractions and 20th and 30th fractions) were statistically significant ($P < 0.05$). The deviations in the ipsilateral parotid gland were slightly greater than that of the contralateral side at each time interval but not reaching statistical significance. The mean volume change for ipsilateral parotid gland decreased from −15.27% at 20th fraction to −37.49% at 30th fraction and partially recovered to −23.14% in 3 months (Fig. 3). There were no significant differences between ipsilateral and contralateral groups despite the changes in the ipsilateral side being relatively greater.

The centroids of both ipsilateral and contralateral parotids moved medially and superiorly during the radiotherapy course with the displacements peaked at 30th fraction and then followed by partial recovery at 3 months after radiotherapy (Fig. 4A–D). The magnitude of displacement in the mediolateral (*x*-axis) direction was the largest, while that of the AP (*y*-axis) direction was the smallest. Although the displacements of the ipsilateral gland were relatively larger than the contralateral side, their differences were not significant.

The shifting of the medial border for both ipsilateral and contralateral parotid glands followed an irregular trend during the treatment course, but in general, it moved laterally from the mid-line (positive change) with magnitudes not greater than 4% (Fig. 5). The lateral border moved medially (negative change) towards the

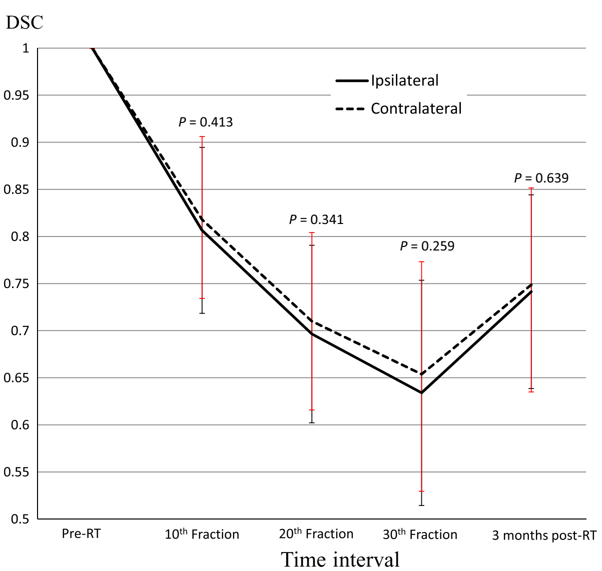

Figure 2. Dice similarity coefficient (DSC) of the parotid gland at various time intervals. Black error bar is for ipsilateral parotid gland and red error bar is for contralateral parotid gland. *P*-values at each time interval are the results of *t*-test between ipsilateral and contralateral glands.

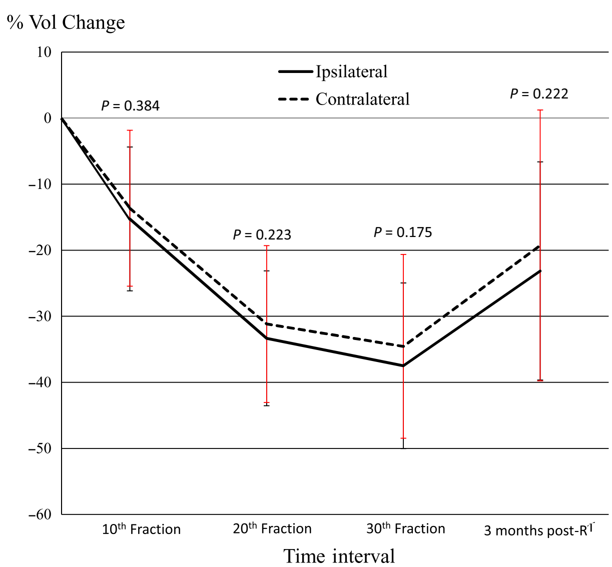

Figure 3. Percentage volume change of the parotid gland at various time intervals. Black error bar is for ipsilateral parotid gland and red error bar is for contralateral parotid gland. *P*-values at each time interval are the results of *t*-test between ipsilateral and contralateral glands.

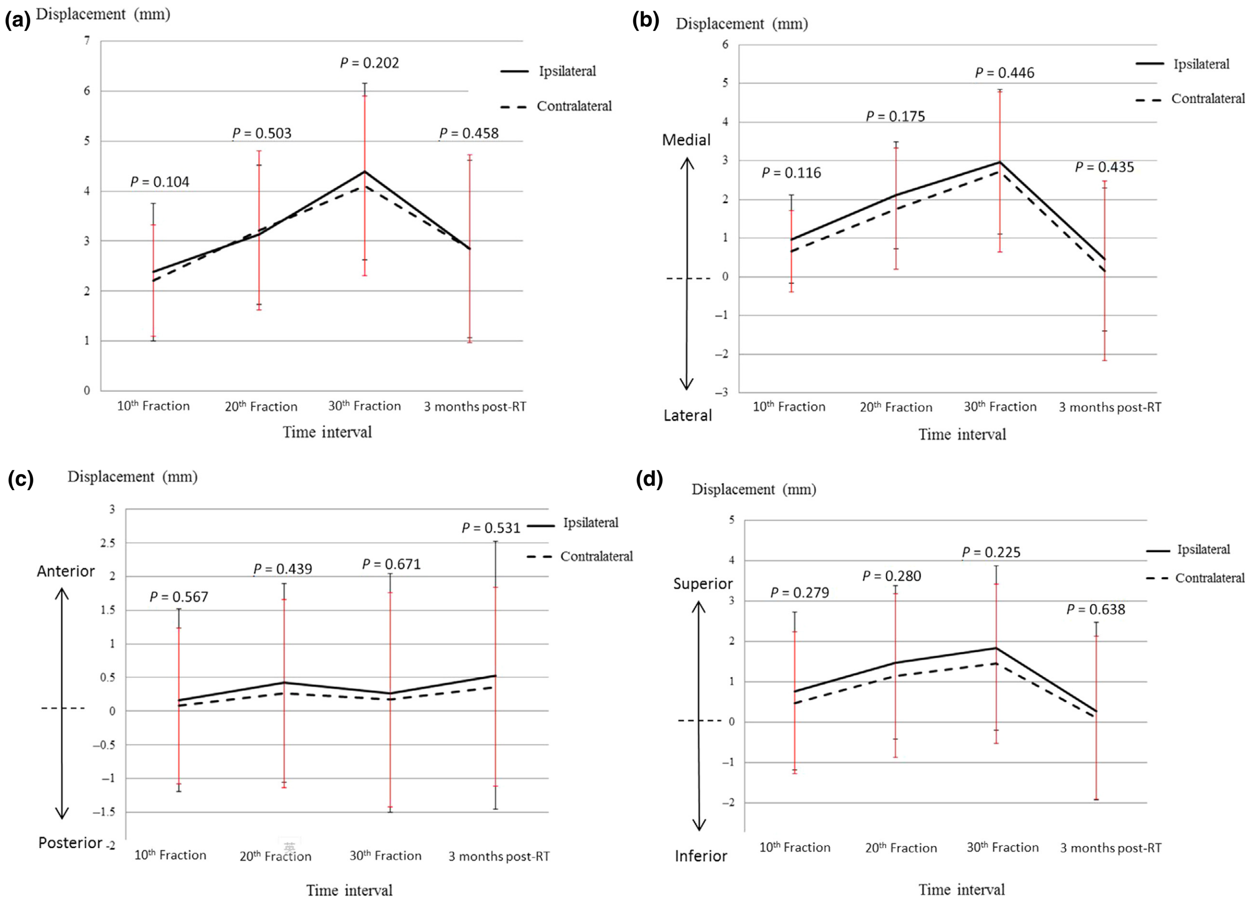

Figure 4. Centroid displacement of the parotid gland at various time intervals. (A) Overall, (B) mediolateral direction, (C) anteroposterior direction and (D) superoinferior direction. Black error bar is for ipsilateral parotid gland and red error bar is for contralateral parotid gland. *P*-values at each time interval are the results of *t*-test between ipsilateral and contralateral glands.

mid-line, in which the ipsilateral gland changed from −3.29% at 10th fraction to −8.58% at 30th fraction and returned to −3.65% at 3 months after radiotherapy. In general, the magnitude of change in the lateral border was greater than that of the medial border. Overall, the magnitude of changes in the ipsilateral side was greater than that of the contralateral side.

Discussion

In our study, the mean dose to the ipsilateral parotid gland was about 5 Gy higher than that of the contralateral side. Both DSC and parotid gland volume demonstrated a decreasing trend during radiotherapy course and recovered to about 75% of the pre-RT values at 3 months after treatment. The average percentage volume changes at the end of the course were −37.49% and −34.55% for ipsilateral and contralateral glands, respectively, implying that both parotid glands had shrunk by about one third of the original volume, which echoed the results of some previous studies.[6,7] The main reason of gland shrinkage was due to the loss and atrophy of acinar cells and granules in the gland,[18,19] which was also believed to be the main cause of xerostomia in patients.[20] Our study revealed that a substantial degree of change of over 30% was observed at around 20th fraction and the parotid glands demonstrated recovery shortly after the completion of radiotherapy, though it was not able to fully restore the original status. The recovery at 3 months after completion of radiotherapy showed that some of the radiation-induced damages to the acinar cells of the parotid gland could be repaired. This implied that the greatest change of the gland took place near the end of the treatment course. It was expected that according to Hey et al.,[21] further recovery of the parotid gland would continue up to 36 months, although full recovery was not likely.

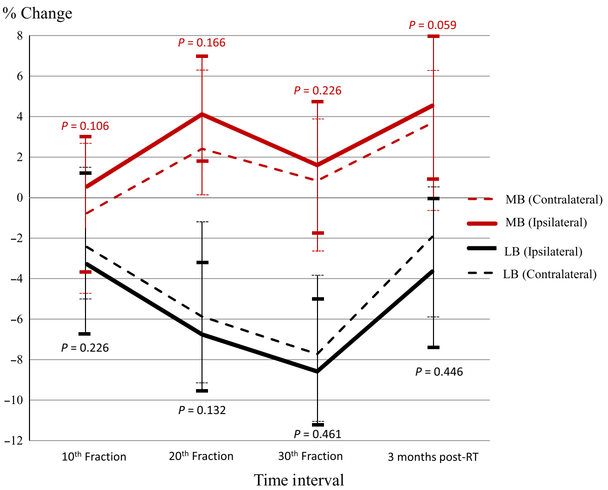

Figure 5. Changes of medial (red) and lateral (black) borders of the parotid gland at various time intervals. Black error bar is for ipsilateral parotid gland and red error bar is for contralateral parotid gland. *P*-values at each time interval are the results of *t*-test between ipsilateral and contralateral glands.

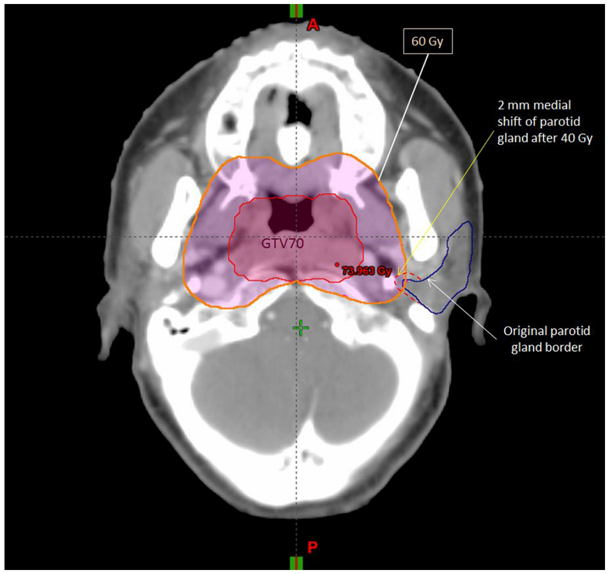

Figure 6. Diagram showing the effect of a 2-mm medial shift of the ipsilateral parotid gland (red dotted line) after 40 Gy. This resulted in a portion of the parotid gland being encompassed by the 60 Gy isodose volume.

In our study, the mean parotid dose in the ipsilateral side was higher than that of the contralateral side. However, the differences in percentage volume changes between these two sides were not statistically significant. One possible explanation was because the mean dose difference between the two sides was not great enough to cause significant difference. Since similar dose constraints were applied to both parotid gland during the optimisation process; added to the fact that tumour of the nasopharynx was centrally situated, the lateral border of the target volume at the contralateral side was still be near to the medial lobe of the parotid gland in many patients; this led to 'less than expected' dose difference between the two sides.

From the results of the centroid displacement, the parotid glands demonstrated an average medial migration during radiotherapy of about 0.3 cm near the end of the treatment course (30th fraction). In addition, the parotid glands also moved superiorly during radiotherapy with an average centroid displacement of about 0.15 cm. The reasons for the mediosuperior migration of parotid glands were twofold. First, since most NPC patients in this region presented with undifferentiated carcinoma of nasopharynx, it is relatively radiosensitive and the radiation delivered to the patient could have caused significant shrinkage of tumour at the PPS, which were situated medially and superiorly to the parotid gland. This might have created space for the parotid glands to move in. Second, the centroid displacement could be partly due to the weight loss of the patients, which was common in NPC patients at the later stage of the treatment course.[22] Weight loss was also present in this cohort of patients as there was a mean reduction of 7.2% in the lateral dimension of the head, as a result most structures would have moved closer to the mid-plane and therefore contributed to the medial shift of the parotid gland. Since the medial migration of the lateral border was comparatively greater than the lateral migration of the medial border, the resultant effect was a medial displacement of the centroid.

When the parotid glands moved medially and superiorly during the radiotherapy course, they might enter into the high-dose zone which was originally planned to cover the PTV including the PPS. An example of this is shown in Figure 6 in which the medial border of the ipsilateral parotid gland showed a 2-mm shift which resulted in an increase of maximum parotid gland dose from 57 Gy to over 60 Gy. Such unexpected high dose delivered to the parotid gland may subsequently increase the risk of xerostomia. Our result was consistent with the studies by Lee et al.[8] and Han et al.[23] They found that the increase in parotid gland dose was highly correlated with their medial displacement towards the high-dose region with the mean dose and V_{26} increased by 11% and 31.3% compared to the original plan respectively. However, this phenomenon would only be important when the mean parotid gland dose is close to its tolerance, for example, 25 Gy as suggested by Deasy et al.,[24] in which additional dose may lead to increase in complication risk. For patients whose original parotid gland dose already exceeds the tolerance, the extra dose due to parotid gland movement may not bear much clinical importance.

Our results indicated that modification of the treatment plan, such as adaptive radiotherapy, was necessary to restore the planned dose to the target and parotid glands, as studies have reported that replanning could reduce the parotid gland dose by 11.2–30.0%.[25,26] It was expected that more frequent replanning could better rectify the dosimetric deviations, but with the expenses of greater resources. An optimal time of replanning is the time when there have been significant changes in the anatomy, but not too late where the new plan will only benefit a few fractions at the end of the course. In our study, substantial changes of both the mean DSC and volume of over 30% in the parotid glands were observed around 10th to 20th fractions time intervals. This echoed the study from Barker et al.[5] who reported that changes in the external contour, shape and location of the structures were significant during the second half of treatment and could have potential dosimetric impact when highly conformal treatment techniques such as IMRT were used. Based on our results, if only one replanning is allowed, we suggested that the most effective replanning time would be at around 15th to 20th fractions. For departments that do not have resources for implementation of adaptive replanning, it would be important to provide an optimal parotid sparing in the initial planning process. Based on the results of this study, margins of 3 mm and 2 mm were suggested to be added at the medial and superior borders of the parotid glands, respectively, to form the planning organ at risk volume before optimisation, so that the parotid gland dose could be kept within tolerance even when there was migration of the organ at the end of the treatment course.

Conclusion

In radiotherapy of NPC patients with PPS involvement, the parotid gland shrank by about one-third towards the end of the treatment course. DSC and percentage volume changes of both ipsilateral and contralateral parotid glands decreased during the radiotherapy course and partially recovered in 3 months after treatment. This trend was also seen in the displacements of centroids and the medial and lateral borders of the gland. Adaptive radiotherapy was suggested at around 15th to 20th fractions so as to reduce the dose to the parotid gland.

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Conflict of Interest

The authors declare no conflict of interest.

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