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Variations of the Dose Distribution Between CT- and CBCT-based Plans for Oropharyngeal Cancer

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Abstract. *Background/Aim: The parotid glands in the head and neck are organs at risks (OARs) adjacent to high dose region and dose of OARs might be increased during the course of radiotherapy. The influence factors of the dose distribution for the parotid glands were investigated in terms of weight loss and mandibular rotation for head and neck cancers treated with volumetric modulated arc therapy (VMAT). Patients and Methods: Ten oropharyngeal cancer patients (OPC) who underwent VMAT were enrolled. The dose volume histogram (DVH) parameters of the parotid glands and planning target volume (PTV) were compared between the planning computed tomography (CT) and the on board imager (OBI) at 1, 5, 10, 15, and 20 fractions. Results: The variation of dose distribution in PTV was not observed in both factors. The relationship between the mandibular rotation and dose difference for the right and left parotid glands (linear regression, r^2=0.1577 and −0.689) showed a slighty stronger correlation with dose difference than the weight loss (linear regression, r^2=−0.079 and −0.547). Conclusion: The mandibular rotation tends to have a large influence on dose distribution of the parotid glands for head and neck cancers treated with VMAT.*

Intensity modulated radiation therapy (IMRT) plays a critical role in the management of head and neck cancer patients (1). IMRT can maximize tumor coverage and/or sparing of organs at risks (OARs) by generating a steep dose gradient, and can thereby lead to a potential increase in the therapeutic index (2, 3). Other parameters, such as fractional anatomical changes, tumor shrinkage, nodal/glandular volume change, weight loss, and geometric variations, which can all occur during a typical 6-7-weeks treatment course (4, 5). A two-step IMRT method used as an adaptive radiation therapy scheme could allow modification of dosing to accommodate changes in body contour, target volumes, and organs at risk during IMRT (6-8). Adaptive radiation matching a change in dose with the patient's condition during treatment is, therefore, important. Cone beam computed tomography (CBCT) can be used to monitor the dose distribution during treatment and confirm the setup (9). Using CBCT obtained from the on-board imager (OBI), the patient's contour can be delineated and its shape and extent changes can be determined using deformable image registration (DIR) from original planning (9-11). For head and neck cancer patients, weight loss and setup accuracy are important, as these influence the dose distribution during IMRT (12-14). Furthermore, setup errors in the neck region of patients are generally greater compared to those occurring in the head region during the course of radiotherapy (15).

In this study, we investigated dose change, weight loss, and setup error (mandibular rotation) in the parotid gland, and used CBCT-based dose calculations to evaluate their influence on the dose distribution for oropharyngeal cancer (OPC) radiotherapy.

Patients and Methods

Patient characteristics and treatment methods. This retrospective study was approved by our institutional ethics committee (approval number:29-124), and all patients provided an informed written consent for volumetric modulated arc therapy (VMAT).

Ten consecutive patients who were treated for OPC using a two-step VMAT method combined with concurrent chemotherapy between November 2015 and August 2016 were evaluated. The tumor and treatment characteristics are shown in Table I.

The technique for two-step VMAT for OPC and the dose constrains have previously been described in detail (16). Briefly, all

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patients were treated with whole neck VMAT to a total of 46-50 Gy in 23-25 fractions as the initial plan, followed by a boost VMAT limited to the high-risk clinical target volume (CTV) of a total dose of 60-70 Gy over 30-35 fractions. All patients were immobilized with a thermoplastic mask covering the head, neck, and shoulders (Fibreplast Head & Shoulder Portrait S-Frame thermoplastic based system; Q-FIX, PA, USA). All treatment planning data for the VMAT were calculated by inverse planning using a commercial treatment-planning system (Eclipse ver.13.6, Varian Medical Systems Inc, CA, USA). The VMAT consisted of 2 arcs. Dose constraints for the VMAT planning used at our institution are described in Table II.

Weekly CBCT and CBCT contouring. All patients were treated by VMAT with weekly CBCT for setup error correction. All images were analyzed online using the Varian On-board Imaging System software (Eclipse) was used to register the planning computed tomography (CT) to the CBCT (1, 5, 10, 15, and 20 fractions) by automatic bone matching. The Planning CT images were reconstructed with a resolution of 0.98×0.98×2.0 mm along the x, y, and z directions respectively. All CBCT images were acquired at a resolution of 0.91×0.91×2.0 mm before the radiation treatment for each fraction. The size of axial images for both planning CT and CBCT was 512×512 pixels. There were 88 slices in each CBCT scan, and the number of slices in the planning CT images ranged from 221 to 311. A total of 20 planning CTs and 100 CBCTs were used in this study. The default parameter settings for the acquisition of the CBCT images were 100 kV and 120 mAs. Using SmartAdapt® DIR software (Varian Medical Systems Inc., Palo Alto, CA, USA), the original planning target volumes (PTVs), CTVs, OARs (parotid glands, spinal cord, and brain stem) and external body contours were propagated to each CBCT for treatment re-planning, taking into account organ deformation (10). The patient's contours were deformed using DIR software and were confirmed by experienced radiation oncologists who were blinded to all other patient and treatment information in this study. The original plan was then copied over to the CBCT images, with the contours deformed for recalculation.

A CT electron density calibration curve was obtained to calculate the dose using CBCT (17). Figure 1 presents the cylindrical water-equivalent phantom (Tough water, Kyoto Kagaku CO., Kyoto, Japan) used to measure the data for this electron density curve. The phantom was 20 cm in diameter and 19.8-cm long, with a central cylindrical hole of 2.85 cm in diameter. Rong *et al*., have reported that the use of a site-specific calibration curve gives a 2% dose agreement with planning CT plans in phantom studies (18-19). Figure 2 shows the Hounsfield unit-electron density (HU-ED) curves of the CBCT and CT scans.

Mandibular rotation. For the image matching between the planning CT and CBCT during VMAT, we focused on the third and fourth cervical vertebrae. The mandibular rotation angle was measured as a setup error. The difference in the mandibular rotation between the planning CT and CBCT was measured from the center of the first cervical vertebrae to the mandible edge (Figure 3) and the average of the left and right values was defined as mandibular rotation.

Analysis. The re-contoured OARs and target volumes were propagated from the planning CT to the CBCT scans using SmartAdapt®. Subsequently, the CBCT plans were constructed with dose calculations obtained using HU-ED curves as shown in Figure 2, with the VMAT plans transferred to the CBCT on the basis of matched isocenters and body alignment. An anisotropic analytical algorithm (AAA) was used for the dose calculations of both original and CBCT plans. To obtain a dose-volume histogram (DVH) for the OARs and targets, the CBCT plans were recalculated without optimization.

The image range (z direction) of the CBCT with a TrueBeam linear accelerator (Varian Medical Systems, Inc., Palo Alto, CA,

Table I. *Treatment characteristics*.

Case	TNM stage	7th edition of UICC stage	Total RT dose	Concurrent chemotherapy
1	c3TN2cM0	IVA	70 Gy	CDDP
2	cT2N2bM0	IVA	70 Gy	CDDP
3	cT3N0M0	III	70 Gy	C-mab
4	cT3N2bM0	IVA	70 Gy	C-mab
5	T2N1M0	III	70 Gy	CDDP
6	cT2N2M0	IVA	70 Gy	CDDP
7	cT2N2bM0	IVA	70 Gy	CDDP
8	T3N0M0	III	60 Gy	C-mab
9	T2N0M0	II	70 Gy	CDDP
10	cT1N2bM0	IVA	70 Gy	C-mab

CBDCA: Carboplatin; C-mab: cetuximab; m: months.

Table II. *The objective parameters used in VMAT optimization*.

Target and risk organs	Dose constraints
PTV (normalized at D95)	D_{98}>93% D_{95}=100% (prescription dose 70 Gy) D_{50}<105% D_{10}<110% D_{2}<120%
Organs at risk	
Brain stem (PRV)	D_{max}<54 Gy
Spinal cord (PRV)	D_{max}<50 Gy D_{1cc}<46 Gy
Optic nerve	D_{mean}<50 Gy
Eyes	D_{mean}<40 Gy
Lens	D_{max}<6 Gy
Inner/middle ear	D_{mean} < 45 Gy
Oral cavity	D_{max} < 30 Gy
Larynx	D_{mean}<20 Gy
Parotid gland (at least one)	D_{mean}<20 Gy
Submandibular gland (at least one)	D_{mean}<35 Gy
Mandible	D_{2}<66 Gy

PTV: Planning target volume; PRV: planning organ at risk volume; Dmax: maximum dose; D_{mean}: mean dose; D_{98}: dose to 98% of the volume; D_{95}: dose to 95% of the volume; D_{50}: dose to 50% of the volume; D_{10}: dose to 10% of the volume; D_{2}: dose to 2% of the volume; D_{1cc}: dose delivered to a 1 cm^3 volume.

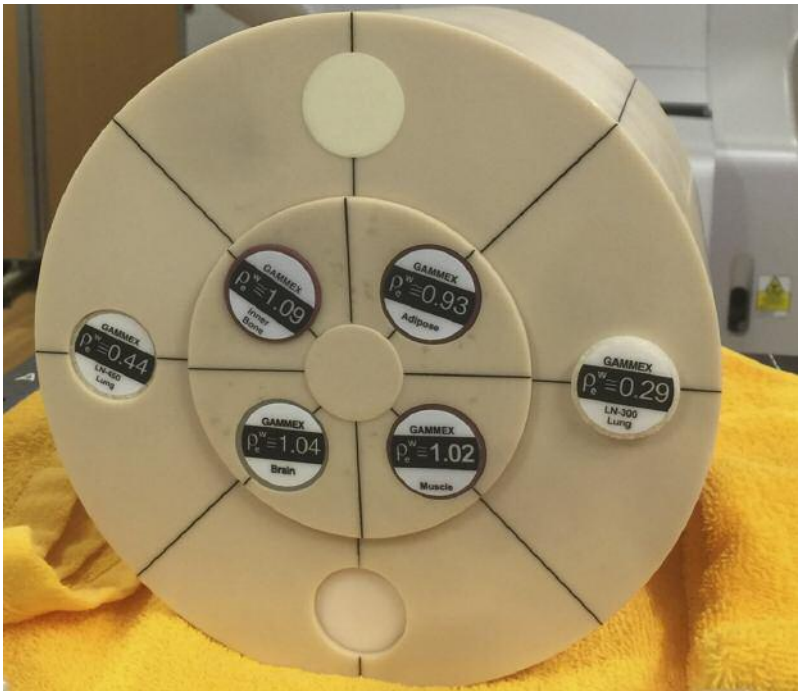

Figure 1. *Frontal view of the head phantom used to simulate the head sites for CBCT dose calculation.*

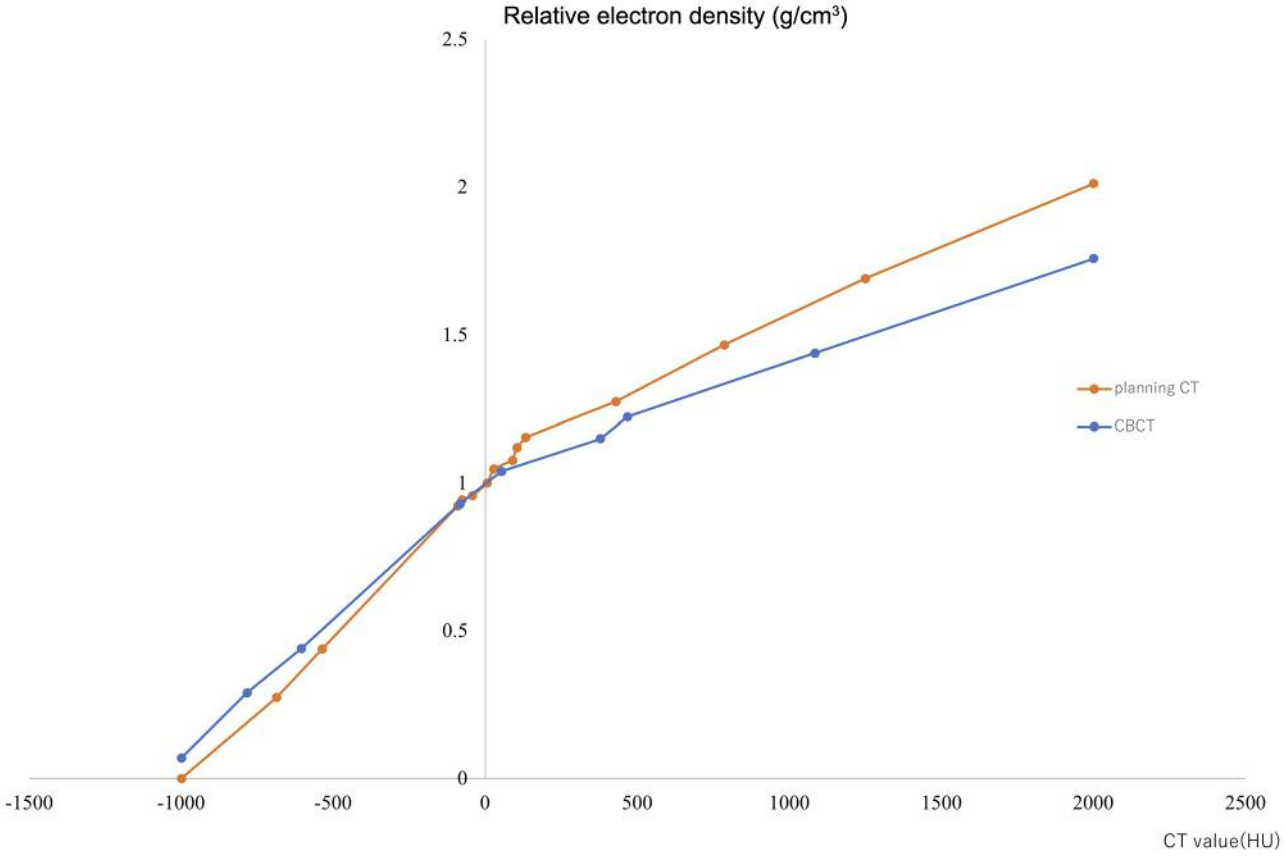

Figure 2. *Comparison of HU-ED curves between the CBCT scans (red line) and planning CT (blue line).*

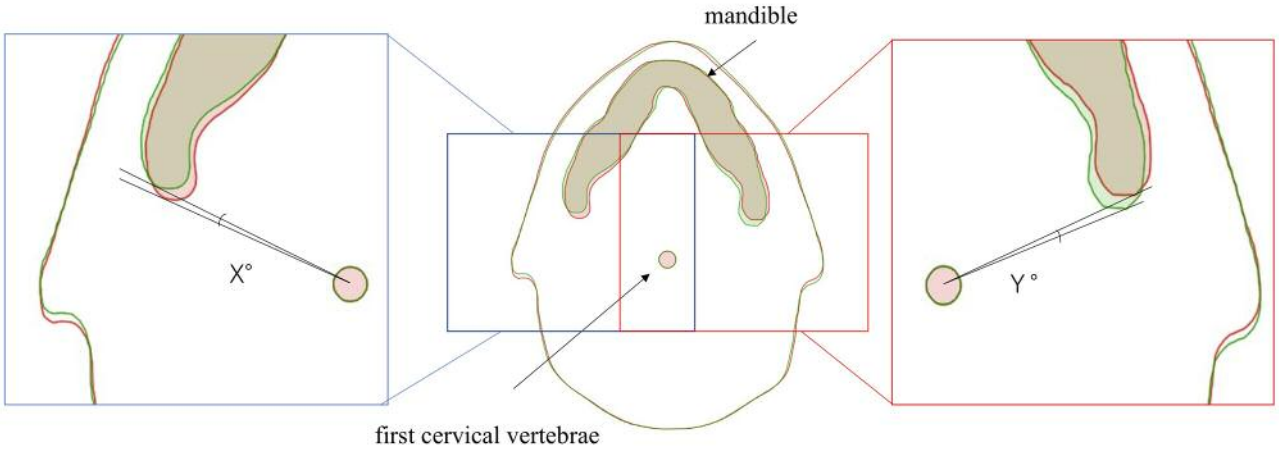

Figure 3. *Measurement of the difference in mandibular rotation between the planning CT and CBCT. Mandibular rotation was measured as the difference between the planning CT and CBCT from the center of the first cervical vertebrae to the mandible edge. The green line represents the CBCT image and the red line represents the planning CT image.*

USA) is limited to 18.8 cm, while the VMAT treatment range has an average of 19.66 cm (range 18.5-23.1 cm), which includes the lower neck. We, therefore, evaluated the DVH only within the image range of the CBCT. The weight of the OPC patient was measured every week during the first VMAT period. Weight loss and the rotation of the mandible were measured, and their influence on the dose distribution was investigated.

Results

The dose difference for the first step VMAT plan and CBCT plans during the first treatment period for the right and left parotid glands are shown in Figure 4A and B, respectively. Figure 4C and D show the time trends for weight change and mandibular rotation during the first treatment period, respectively. The dose difference to both parotid glands fluctuated over the course of the treatment is shown in Figure 5. The maximum weight loss was 8.9 kg. Figure 5A and B show the relationship between the weight loss and dose difference for the right and left parotid glands (slopes of −0.1092 and −0.5974, respectively, with linear regression, and r^2=−0.079 and −0.547) during the first treatment. Figures 5C and D show the relationship between mandibular rotation and dose difference for the right and left parotid glands (slope of −0.5794 and 0.9226 with linear regression, r^2=0.1577 and −0.689, respectively) during the first VMAT treatment. The mean dose of left parotid glands and mandibular rotation showed no correlation with dose variation. In both mean doses of the right and left parotid glands, mandibular rotation showed a much stronger correlation with dose difference than did weight loss. On the other hand, the variation of dose distribution in PTV was not observed in both factors during the course of radiotherapy.

Discussion

In this study, an increased likelihood of larger dose variations was shown to be associated with mandibular rotation during the course of radiotherapy. The weight loss is a significant factor changing the dose distribution during the course of IMRT for head and neck cancers, and requires re-planning (20). However, our data revealed unexpected dose changes that could not be explained by weight loss alone and these unexpected dose changes were due to mandibular rotation (Figure 5). The accuracy of the setup was shown to have a greater impact on the dose distribution to the parotid gland compared to weight loss. Castelli *et al*. described that variation in the mean parotid gland dose was more important between the planning CT and the CT for fraction 1 than between each weekly CT (21). This difference may be explained by the delay between the planning CT and the first CBCT. Parotid gland dose differences between the fraction and the initial planning are likely to be related to both setup errors and variations in the volume and shape of anatomical structures. Systematic setup errors may increase the mean parotid gland dose by around 3% per mm of displacement (21-23).

A highly accurate setup is necessary during VMAT, ideally with the same patient status being maintained throughout the treatment. However, a patient's physical status can dramatically change over the treatment period due to weight loss and/or tumor shrinkage. Such considerable anatomical changes during the course of radiotherapy may lead to suboptimal dosing (20). Bhide *et al*., have also reported that weight loss and anatomical changes are associated with changes in dose distribution (24). Minimization of the daily setup error could in fact reduce the irradiated doses to the parotid glands, resulting in improvements

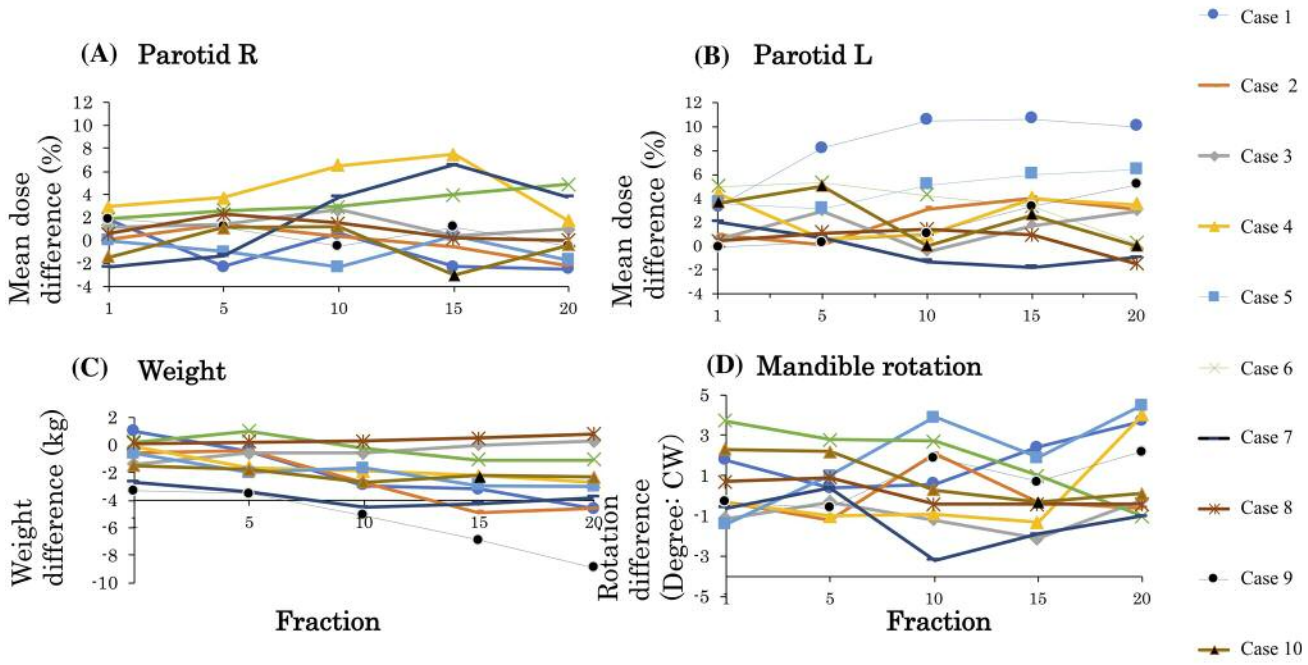

Figure 4. *Time trends of the dose differences of the first step of the VMAT and CBCT plans (1, 5, 10 15, and 20 fractions) for right (A) and left parotid gland (B). Time trends of weight (C) and mandibular rotation (D) during the first VMAT.*

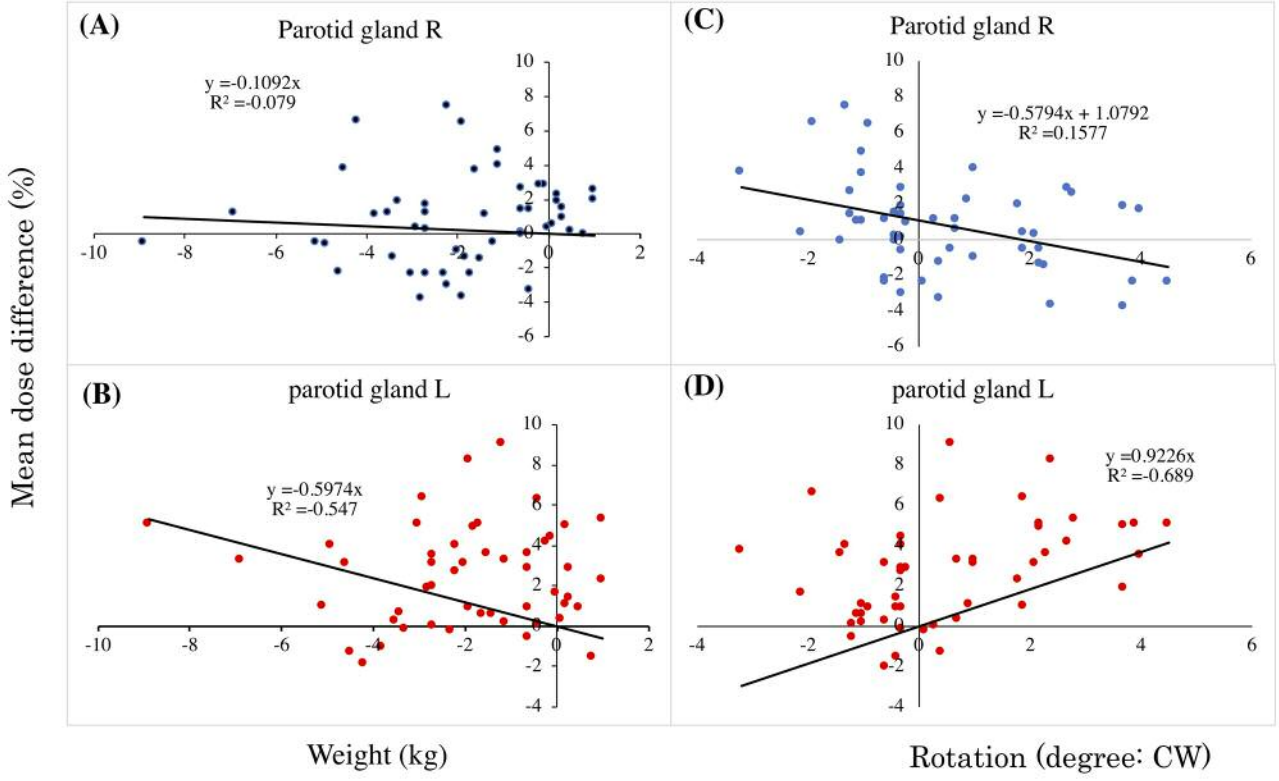

Figure 5. *Relationship between weight and dose difference for right (A) and left parotid gland (B) during the first VMAT treatment. Relationship between mandible rotation and dose difference for right (C) and left parotid gland (D) during first VMAT treatment.*

to patients' quality of life and toxicity risk (7). The points suggest that a combination of bone registrations to correct for setup errors and re-planning to correct for anatomical variations is necessary in daily practice.

Knowledge-based planning (KBP), which was developed and released for clinical use (25-27), can reduce the optimization time of re-planning for adaptive radiation therapy. Adaptive radiotherapy is especially important in IMRT and VMAT for head and neck cancers, where the effects of setup errors with respect to unexpected dose distributions are poorly understood. For adaptive radiation therapy using KBP, the patient setup is an important factor for IMRT, with strategies for ensuring accurate patient setup being necessary at CT simulation and during the course of radiotherapy. To provide consistent dose contributions in patients who need adaptive radiotherapy, not only is re-planning required, but also a highly accurate patient setup is major importance.

This study is subject to certain limitations. The CBCT imaging range did not cover the entire treatment areas of the VMAT. Sparing the parotid glands is an important reason for using IMRT (7). Furthermore, this retrospective study includes only a small number of patients with heterogeneous characteristics. Therefore, further prospective CBCT studies covering the entire range of VMAT adaptive treatments are required to establish the ideal fixation and onboard validation methods for head and neck VMAT. In VMAT for OPC, setup is an important factor for both the initial CT simulations and the treatment. Improving the setup can contribute to achieving a highly consistent dose distribution during the entire VMAT treatment course for head and neck cancer.

Conflicts of Interest

The Authors report no conflicts of interest. The authors are responsible for the content and writing of the paper.

Authors' Contributions

Concept and design were performed by MO, KI, and HM. Experiments were performed by MO and KM, data analysis by MO and HM, and manuscript preparation by MO, MT, HD, YN, and HM. All authors read and approved the final manuscript.

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