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Therapeutic dose effects of target-volume changes during head and neck radiotherapy

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ABSTRACT

Background: Due to the complicated dose calculations, in volumetric modulated arc therapy (VMAT), treatment errors may occur with changes around the lesion due to changes in the patient volume. The head and neck contain many major organs at risks (OAR)s increasing the likelihood of volume changes in OARs due to the effects of radiotherapy. ***Materials and Methods:*** The dose distribution and effects according to the changes in patient volume were analyzed while maintaining the same beam and irradiation conditions as in the initial treatment plan. The volume was extracted to quantify the volume change by setting the region of interest (ROI) of a fan-shaped area formed tangentially to the planning target volume (PTV), with the spinal cord as the center in the transverse plane. ***Results:*** As the radiation treatment progressed, the head and neck volume changes accelerated. As the volume change increased, the target's low-dose distribution area, the incident dose to the spinal cord and parotid gland, and the incident dose to the target periphery increased. In particular, an increase in the target's cold spot and the incident dose to the parotid gland can cause late effects as well as insufficient treatment. ***Conclusion:*** The alteration in dose distribution can be anticipated by monitoring the shift in patient volume using the ROI extraction method outlined in this study.

INTRODUCTION

Modern radiation therapy technology has advanced through the development and use of high dose and high-precision approaches. Intensity-modulated radiation therapy (IMRT), introduced in the early 2000s, is a widely used treatment technique that has enabled these advancements [1-4]. On the other hand, volumetric modulated arc therapy (VMAT), which employs multiple beam directions and can dynamically deliver doses during gantry rotation, has allowed improvements in accuracy and speed [5, 6]. VMAT is excellent for intensive treatment of tumors and protection of surrounding normal tissues by realizing complex radiation intensity profiles from many angles. However, since it is fundamentally based on complex dose calculations, changes around the lesion due to changes in the patient's volume may cause fatal treatment errors [7, 8]. In addition, prediction of changes in the dose distribution caused by treatment errors is difficult in VMAT [9].

The findings of the volume change analysis and treatment replanning patterns over the course of one year at our research institute demonstrated that 57.5% of volume changes and 43.7% of treatment replanning cases occurred in the head and neck region. Several studies have reported changes in dose distribution in relation to volume changes in patients with head and neck cancer [10,11]. In addition, other studies have reported changes in the parotid gland, etc., in relation to volume changes and treatment progress [12-15]. Therefore, in addition to causing changes in the lesions through their therapeutic effects, radiation therapy can also cause change in normal tissue, such as weight loss due to difficulties in food intake attributable to the side effects on the esophagus and oropharynx and reduction of the parotid gland [16-18].

The radiation treatment process generally involves examination/prescription, treatment computed tomography (CT) scan, treatment plan, cone-beam CT (CBCT) scans for patient setup, and treatment. The CBCT scan for the patient setup was

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compared with the CT image used in the initial treatment plan to observe treatment position adjustments and treatment effects on the target and changes in the patient's volume. If a change in the dose distribution in the initial treatment plan was expected due to changes in the patient's volume, treatment replanning was performed. In general, volume changes are periodically checked in the field by performing CBCT scans with the treatment equipment. However, because these changes are evaluated using visual inspections of in 2D images obtained in the sagittal, coronal, and transverse planes, it is challenging to confirm volume changes intuitively, and changes in dose distribution are more difficult to ascertain.

Various studies have been conducted to confirm the changes in dose distribution, e.g., by using megavoltage CT (MVCT) or CBCT to check patient setup errors and performing calculations or using machine learning [19-22]. However, these approaches have still not been actively applied to the treatment field. This means that in clinical practice, the only available choices are to either discontinue treatment or replanning based on subjective and empirical judgment, which can lead to a reduction in the quality of treatment. In clinical practice, the only possible choice is to stop or replan treatment based on subjective and empirical judgment, which may deteriorate the quality of treatment.

The objective of this study was to interpret the dose distribution according to the change in patient volume to provide an objective basis for decision-making. Therefore, In this study, we evaluated the head and neck patients showing the highest frequency of patient volume changes and treatment replanning to confirm the changes in dose distribution in relation to volume changes. In addition, the effects on the target, normal tissue near the target, and major organs at risks (OAR)s in relation to the treatment date and volume changes were analyzed.

MATERIALS AND METHODS

Dose calculation for volume change

Figure 1(a) shows the radiation treatment process, and CBCT scans were conducted for each radiation treatment to observe the patient's volume change. The treatment replanning is determined based on the observed volume change in the treatment area, the volume change in the adjacent area, and the patient's weight change. Therefore, in this study, to observe the change in treatment dose distribution according to patient volume change, CT images obtained for treatment re-planning were used to recalculate the dose distribution for the CT images of treatment re-planning with the same beam and irradiation conditions used in the initial treatment plan. The CT images used in this study were obtained with a 16-low spiral CT scanner (LightSpeed, GE, USA).

This study was limited to the head and neck site with the largest number of patient volume changes and treatment re-plannings. Cases in which treatment replanning occurred due to changes in the patient's volume during treatment were selected. Figure 1(b) shows an example of a case in which the dose distribution changed in relation to patient volume changes under the same beam and irradiation conditions as in the initial treatment plan. When the dose distribution calculated in the initial CT is applied identically to the subsequent CT where volume change occurs, it can be confirmed that an unintended dose occurs. Furthermore, it can be confirmed that there is a discrepancy between the dose distribution calculated for the subsequent CT and the dose distribution of the initial CT. Therefore, the patient in figure 1(c) lost 5 kg of weight and showed a reduction of approximately 10% in the head and neck volume over 20 days. In particular, because the changes in the patient's volume were not uniform, hot and cold spots occurred in the target volume and surrounding areas. The findings confirmed that unintended doses were incident on the normal tissues and major OARs.

This study used the Elekta Monaco treatment planning system (TPS; Elekta, Crawley, UK), a Monte Carlo-based commercial dose-calculation program. In addition, while maintaining the same beam and irradiation conditions as in the initial treatment plan, the dose distribution and effect according to the patient volume change were analyzed. The head and neck plans were generated using three full arcs with 6-MV photon beams of the Versa HD (Elekta, Crawley, UK).

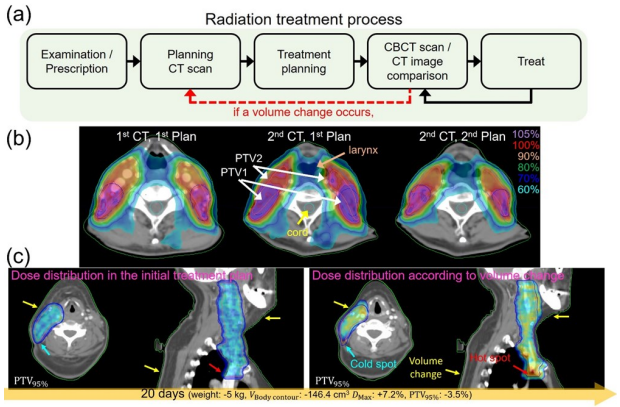

Figure 1. (a) Schematic diagram illustrating the radiation treatment process, **(b)** sample planning images of dose distribution changes and modified dose distribution with volume change, and **(c)** comparison of the dose distribution in the initial treatment plan and the dose distribution based on the volume change after 20 days. Abbreviations: $PTV9_{5\%}$=95% of prescription dose in PTV, PTV = planning target dose, V=volume, D_{Max}= maximum dose.

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Method for calculating volume change

During the treatment using VMAT, most of irradiation is performed at angles that include the planning target volume (PTV) area based on the isocenter. Moreover, the majority of the dose is concentrated on the target, resulting in a markedly reduced dose within the rotation radius that excludes the target in comparison to the dose within the rotation radius that includes the target. Therefore, considering that the change in the patient volume within the rotation radius that does not include the target is minimal, in this study, the volume of the fan-shaped region formed tangential to the PTV centered on the spinal cord among the body regions of the transverse plane including the PTV, as shown in figure 2(a), was extracted. In addition, an OAR dose-distribution change analysis was performed by considering only the area of the transverse plane, including the PTV. Region of interest (ROI) extraction and volume calculations were performed using our in-house software (MATLAB, MathWorks, USA).

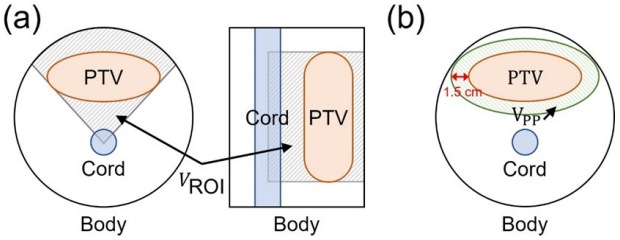

Figure 2. Calculations of volume and target, normal tissue, and OAR dose distribution. **(a)** ROI for volume change analysis, and **(b)** PTV and surrounding normal tissue region for dose distribution change analysis. Abbreviations: OAR = organ at risk, ROI = region of interest, PTV = planning target volume.

Patient characteristics

The 18 patients whose volume changes were observed consisted of 16 males and 2 females, and their ages ranged from 44 to 74 years (table 1). All the sites were in the head and neck, and concurrent chemoradiation therapy (CCRT) was performed in 17 patients. The total prescription dose was 60 Gy (2 Gy/fraction) in 2 cases and 70 Gy (2 Gy/fraction) in 16 cases. The rationale for conducting a second CT scan was based on the observation of tumor shrinkage in 6 cases, body shrinkage in 10 cases, and weight loss in 2 cases. The second CT scan was performed between 10 and 28 days after the initial CT scan. However, most second CT scans were conducted around the 20th day. The ROI volume change exhibited a range of 22.5 to 195.6 cm^3. However, following the performance of a second CT scan due to body shrinkage and weight loss, the ROI volume change often demonstrated a value lower than 100 cm^3. All clinical information was investigated after obtaining the approval with exemption of the institutional review board of Pusan National University Yangsan Hospital (IRB approval numbers: 05-2023-018).

Table 1. Patient characteristics.

ID	Age/ gender	Stage	Primary site	Prescrip-tion dose	Indication for 2nd scan	Time until 2nd scan	ΔV_{ROI} (cm^3)
1	44/M	T4N2b	NPX	60	Tumor	15	78.8
2	71/M	T3N2	NPX	70	Body	24	57.6
3	65/M	T4N2c	NPX	70	Tumor	18	106.5
4	65/M	T3N2	NPX	70	Weight	17	51.4
5	72/M	T3N3b	BOT	70	Tumor	25	123.1
6	72/M	T1N2	BOT	70	Body	22	99.2
7	59/M	T3N1	NPX	70	Body	24	61.2
8	48/M	T2N1	Rt. Tonsil	70	Tumor	19	133.7
9	62/M	T2N0	Glottis	70	Body	10	43.7
10	61/M	T4N0	Glottis	70	Tumor	28	75.5
11	74/F	T4N2c	BOT	70	Body	22	22.5
12	58/M	T1N1	NPX	70	Body	22	100.5
13	48/M	T4aN0	NPX	60	Body	25	115.6
14	73/M	T3aN3b	BOT	70	Body	22	195.6
15	64/M	TxN2c	BOT	70	Tumor	12	102.7
16	62/M	T2N3	NPX	70	Body	17	77.7
17	68/F	T4N1	NPX	70	Body	25	130.9
18	74/M	TxN2b	BOT	70	Weight	25	158.7

Abbreviations: ID = identification number; M = male; F = female; NPX = nasopharynx; BOT = base of tongue, Rt. = right, ΔV_{ROI} = ROI volume change.

Statistical analysis

This study evaluated changes in PTV and OARs by analyzing dose distribution according to volume change, utilizing the dose-volume histogram (DVH) statistical function provided by the Elekta Monaco TPS (Elekta, Crawley, UK). Furthermore, as shown in figure 2(b), we attempted to observe the changes in the dose distribution in the PTV periphery volume (VPP). VPP is a donut-shaped volume excluding the PTV with a 1.5 cm margin in all directions from the PTV, and the effect on the normal tissue adjacent to the target was analyzed by assessing the VPP. Using this approach, we tried to confirm the effects of the volume-related shifting and changes in the dose distribution on the periphery. The brain stem, spinal cord, esophagus, and parotid gland were selected as the major OARs.

The objective was to analyze PTV from a radiation therapy perspective by evaluating the coverage change at 100%, 95%, and 90% of the prescribed dose. Additionally, the maximum, average, and minimum dose changes of the PTV were evaluated. From an organ protection perspective, VPP assessed the 95%, 80%, and 50% dose changes relative to the prescribed dose, while the major OARs examined the maximum, mean, and minimum dose changes per fraction. In this study, statistical analysis was conducted using our in-house software (MATLAB, MathWorks, USA).

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RESULTS

Target dose distribution with volume change

The coverage by prescription dose ratio of the PTV in relation to volume reduction can be confirmed in figure 3(a), (b), and (c). $D_{k\%}^{Rx}$ is the dose corresponding to k% of the prescribed dose, and the formulas for the amount of change (e.g., ΔC, ΔV, ΔD and) in this study were derived by subtracting the initial value from the change value (e.g., $\Delta C = C_{V\ changed} - C_{V\ initial}$). The greater the reduction in volume, the greater the tendency to decrease in comparison with the existing dose distribution. In addition, the findings confirmed that coverage decreased as the prescribed dose approaches. This is because a cold spot occurs in the PTV, or an area with a dose distribution less than the intended dose distribution in the PTV was increased.

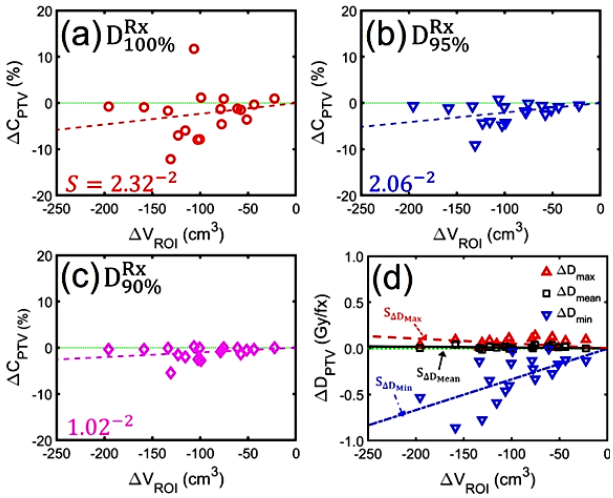

Figure 3. PTV coverage and dose distribution of the PTV for the prescription dose ratio in relation to VROI changes. **(a)** PTV coverage at 100% of the prescription dose, **(b)** PTV coverage at 95% of the prescription dose, **(c)** PTV coverage at 90% of the prescription dose, and **(d)** changes in the maximum, minimum, and average dose in the PTV. Abbreviations: $D_{k\%}^{Rx}$=prescription dose ratio of the PTV, ΔC_{PTV}=PTV coverage changes, ΔD_{PTV}=PTV dose changes, ΔV_{ROI}=ROI volume changes, ROI=region of interest, PTV=planning target volume.

The changes in the maximum, minimum, and average PTV doses in relation to the volume change are shown in figure 3(d). The maximum dose tended to increase as volume decreased. Thus, while the average dose did not change significantly, the minimum dose decreased considerably with a reduction in volume. As the volume decreased, the area inside the PTV with a dose distribution smaller than the prescribed dose increased, and the cold spot increased. In addition, the trend line was fitted with a linear function by setting the dose change to zero when the volume change was zero, and the slope of the minimum dose change was confirmed to be steep. It is important to note that any unintended changes to the volume may result in disruptions to the overall dose distribution, potentially leading to the formation of hot spots or cold spots. This also demonstrates that the dose distribution of the PTV, as calculated by the initial treatment plan, is subject to alteration by the volume that has changed due to the discrepancy in the percentage depth dose curve (PDD) of the X-ray. In essence, the larger the volume change, the greater the challenge in delivering precise radiation therapy to the designated treatment area.

Figure 4 shows the volume by the prescription dose ratio of the PTV periphery (PP) in relation to the volume reduction. Figure 4(a) shows the 95% coverage of the prescription dose. As the volume decreased, the dose to be incident on the PTV spread to the PP, and the dose incident on the PP area increased. Figure 4(b) shows the change in 80% coverage of the prescription dose in PP, which also increased. As shown in figure 4(c), the dose change around the PTV became insignificant with respect to the volume change at 50% coverage of the prescription dose. Although the dose was precisely distributed along the PTV boundary through dose calculation using VMAT, a new boundary was judged to have been created owing to irregular volume change, adversely affecting the inside and outside of the PTV.

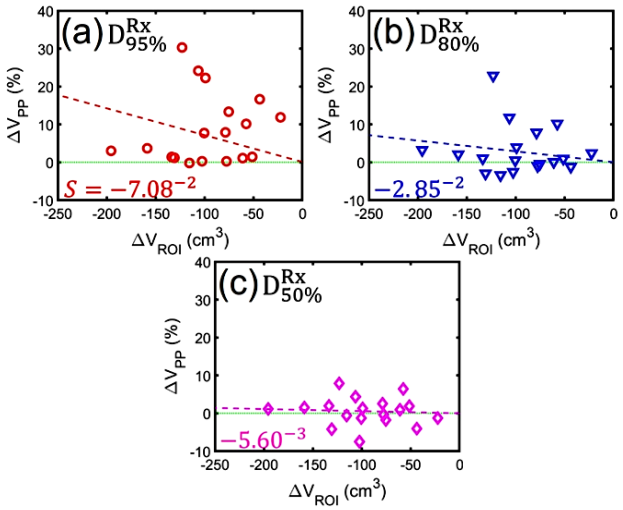

Figure 4. VPP for the prescription dose ratio in relation to the VROI change: **(a)** 95% of the prescription dose, **(b)** 80% of the prescription dose, and **(c)** 50% of the prescription dose. Abbreviations: $D_{k\%}^{Rx}$ = prescription dose ratio of the PTV, ΔV_{PP} = PTV periphery volume changes, ΔV_{ROI} = ROI volume changes, ROI = region of interest, PTV = planning target volume.

Major OARs dose changes with volume change

The changes in the incident dose to the major OARs in relation to the volume changes are shown in figure 5. For the brain stem in figure 5(a), the data from 16 of 18 patients were used, and the change in the maximum dose overall increased in relation to the change in volume. In some patients, the change in the minimum and average doses was significantly reduced, and no significant trend was found in relation to the change in patient volume. This is because the brain stem is located in an area where the volume is not easily changed because of the skull.

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Figure 5(b) describes the change in the incident dose to the spinal cord according to the volume change, and the findings confirmed that all incident doses increased overall. In particular, the increase in the maximum dose was conspicuous. The spinal cord, for which consistency of the maximum dose is emphasized, is sensitive to volume changes.

Figure 5(c) shows the changes in the incident dose to the esophagus in relation to the volume change. The maximum and average dose changes tended to increase, while the minimum dose change tended to decrease. Thus, the esophagus seemed to be sensitive to volume changes in the neck region, which shows a lot of volume changes because the esophagus is located below the neck region, but the effects in the chest region, which does not show much volume change, were fewer.

Figure 5(d) shows the changes in the incident dose to the parotid gland in relation to the volume change, and all doses were found to have increased. This was most affected by volume changes because the lesions of patients with head and neck cancer usually contained or were adjacent to the parotid gland.

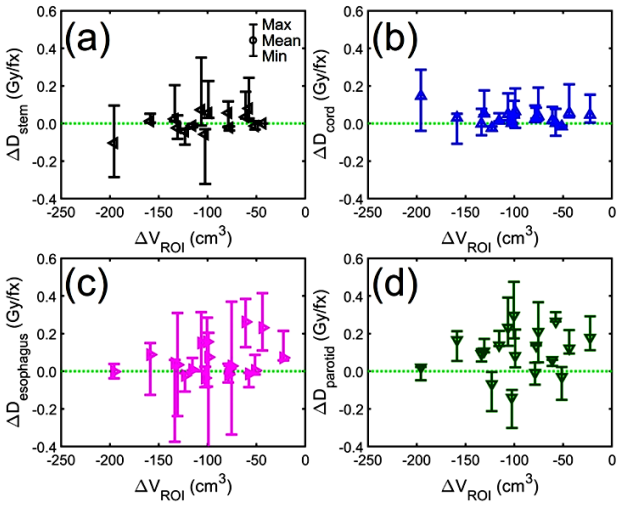

Figure 5. Dose change in OARs with the change in VROI. **(a)** The brain stem, **(b)** spinal cord, **(c)** esophagus, and **(d)** parotid gland. Abbreviations: ΔV_{OAR} = specific OAR dose change, OAR = organ at risk, ΔV_{ROI} = ROI volume changes, ROI = region of interest, PTV = planning target volume.

The average values of the maximum, minimum, and average doses to the OARs are shown in figure 6. The OARs showed an overall increase in dose change, and the dose increase in the spinal cord and parotid gland, among the OARs, was remarkable. Because of the signature rotational treatment in VMAT, the volume change was sensitive to the change in dose distribution; therefore, the OAR adjacent to the PTV or the OAR included in the incident angle in the treatment plan may have been greatly affected. It can be concluded that the volume change increases the maximum dose of the brain stem and spinal cord, and increases the mean dose of the esophagus and the parotid gland. The brain stem and spinal cord have DVH limits corresponding to the maximum dose, while the esophagus and parotid gland have DVH limits corresponding to the mean dose. It indicates that the DVH limits of the major OARs close to the treatment area may be surpassed due to volume changes.

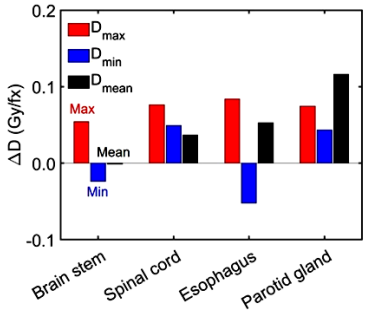

Figure 6. The average value of the maximum, minimum, and average dose changes for the brain stem, spinal cord, esophagus, and parotid gland. Abbreviations: ΔD = dose change, D = dose.

Figure 7 shows the volume change in relation to the treatment period. The volume decreased as treatment progressed to 2 Gy per fraction. The volume change with the treatment showed a generally linear decrease. Upon examination of the results depicted in figures 3-5, it was observed that the dose distribution changes for PTV and major OARs exhibited an increase when the volume change reached -100 cm^3 or greater. This means treatment re-planning should be considered for treatment periods exceeding 20 days or changes exceeding 100 cm^3 based on ΔV_{ROI}.

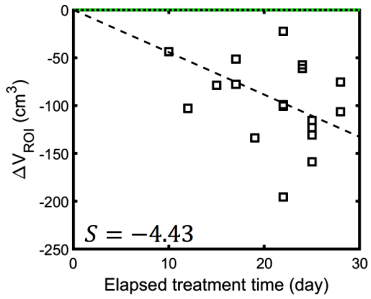

Figure7. VROI volumetric change rate results as a function of the elapsed treatment time. Abbreviations: ΔV_{ROI} = ROI volume changes.

DISCUSSION

The small area of the head and neck includes many OARs, and many OARs are included in or adjacent to the PTV. In head and neck radiotherapy, the major OARs where dose distribution changes were observed due to volume changes included the spinal cord, brain stem, and parotid gland. It has been reported that treatment replanning, taking into account these volume changes, can lead to an improvement in the maximum dose [23]. The mean dose to the spinal cord appears to be unaffected by volume changes; however, cases where the maximum

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point dose significantly increased were observed. Other studies have similarly reported that the mean dose to the spinal cord does not change substantially due to volume changes [24]. However, it was frequently observed that the distance between the spinal cord and the PTV was small (0.8–2.0 cm) or that the PTV encompassed the spinal cord. Volume reduction may decrease the distance that X-ray beams travel from the body surface to the spinal cord, potentially causing adverse effects on the spinal cord. Since the spinal cord has strict dose limits for the maximum dose in the DVH, careful attention is required. In particular, a reduction in the volume of the parotid gland during head and neck radiotherapy has been reported in numerous studies, with findings indicating an average volume reduction rate of 30–44% [7, 11, 15, 25]. As demonstrated in the results of this study, the parotid gland was the OAR that experienced the most significant volume reduction. This is largely attributable to the frequent inclusion of the parotid gland within the PTV, leading to substantial exposure to radiation. In terms of the DVH limits, the average dose to the parotid gland is considered important; however, the parotid gland can be a difficult-to-protect OAR in some cases. Nevertheless, since an increase in the dose to the parotid gland may cause discomfort to the patient due to late effects such as dry mouth [26-30], the changes in the dose to the parotid gland in relation to volume changes cannot be ignored.

The target volume showed significant changes, comparable to those observed in the parotid gland. This phenomenon has also been widely reported in the literature, with studies indicating that the gross tumor volume (GTV) can decrease by as much as 70% [7, 11, 25, 31, 32]. Additionally, the GTV often exhibited asymmetric changes in volume [7]. Similarly, in this study, substantial alterations in the dose distribution and coverage of the target were observed in response to these volumetric changes. This also suggests that the reduction of the target may significantly increase unnecessary dose distribution around the target periphery.

Patient weight loss is a factor that necessitates consideration of treatment replanning and can also serve as a crucial indicator for predicting volumetric changes in the patient. Accordingly, several studies have described the relationship between weight loss and dose variations in the target and organs-at-risk (OARs) [7, 32]. However, even in studies aimed at minimizing weight loss, volumetric changes in the target and parotid gland were observed [31]. In this study, the patient's body weight decreased by an average of 3.42 kg during the treatment period, but it ranged from a minimum of 0.4 kg to a maximum of 10 kg. These weight changes were excluded from the analysis because we could not find a correlation of volume changes with the weight change [31, 32]. The relationship between the elapsed treatment time and volume changes was demonstrated through studies reporting that volume changes and dose variations in the target and OAR occurred during the 2nd and 3rd weeks of treatment [7, 11, 15]. This study also identified a linear relationship between the elapsed treatment time and volume changes, with a notable increase in the maximum dose observed around 20 days into treatment (cumulative dose exceeding 40 Gy), indicating a higher dose delivery to the PP. These findings suggest that if the volume change reaches 100 cm^3 or the treatment duration exceeds 20 days, treatment replanning could be beneficial to accommodate the significant alterations in the dose distribution for the PTV and OARs. Furthermore, continuous monitoring of volume changes is anticipated to greatly enhance the accuracy and precision of radiotherapy.

CONCLUSION

Over the course of radiation treatment, the head and neck volume changes accelerated, and the target low-dose distribution area increased with an increase in the volume change, confirming an increase in the incident dose to the spinal cord and parotid gland. The degree of volume change may vary depending on the treatment environment, treatment equipment, and the radiation sensitivity of the patient. With the ROI extraction method presented in this study, it will be possible to calculate the patient volume from CBCT, which is used for patient settings during radiation therapy and lacks field-of-view. In addition, this method can be used in further studies to calculate the dose distribution according to the volume changes in CBCT and to determine the cumulative dose.

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***Ethics approval*:** All clinical information was investigated after obtaining the approval with exemption of the institutional review board of Pusan National University Yangsan Hospital (IRB approval numbers: 05-2023-018).

***Conflicts of interests*:** All authors declare that they have no conflicts of interests.

***Author contribution*:** All authors participated in research and preparation of manuscript and its final approval for submission equally.

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