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Usability of Deformable Image Registration for Adaptive Radiotherapy in Head and Neck Cancer and an Automatic Prediction of Replanning

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Abstract

Deformable image registration (DIR) has been an important component in adaptive radiotherapy (ART). Our goal was to examine the accuracy of ART using the dice similarity coefficient (DSC) and to determine the optimal timing of replanning. A total of 22 patients who underwent volume modulated arc therapy (VMAT) for head and neck (H&N) cancers were prospectively analyzed. The planning target volume (PTV) was to receive a total of 70 Gy in 33 fractions. A second planning CT scan (rescan) was performed at the 15th fraction. The DSC was calculated for each structure on both CT scans. The continuous variables to predict the need for replanning were assessed. The optimal cut-off value was determined using receiver operating characteristic (ROC) curve analysis. In the correlation between body weight loss and DSC of each structure, weight loss correlated negatively with DSC of the whole face ($r_s = -0.45$) and the face surface ($r_s = -0.51$). Patients who required replanning tended to have experienced rapid weight loss. The threshold DSC was 0.98 and 0.60 in the whole face and the face surface, respectively. Patients who showed low DSC in the whole face and the face surface required replanning at a significantly high rate ($P < 0.05$ and $P < 0.01$). Weight loss correlated with DSC in both the whole face and the face surface ($P < 0.05$ and $P < 0.05$). The DSC values in the face predicted the need for replanning. In addition, weight loss tended to correlate with DSC. DIR during ART was found to be a useful tool for replanning.

Keywords

Deformable Image Registration, Adaptive Radiotherapy, Head and Neck

Cancer, Dice Similarity Coefficient, Volume Modulated Arc Therapy

1. Introduction

Modern radiotherapeutic techniques, such as intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) are considered the standard radiotherapy techniques for the treatment of head and neck squamous cell carcinomas (HNSCC) [1] [2] [3] [4]. These techniques enable delivery of high radiation doses to tumor volumes with reduction of exposure to organs at risk (OARs) [2]. However, geometric and anatomical changes that can occur over a treatment course include tumor and nodal shrinkage, changes in tumor position, and weight loss. This can result in the need to recalculate dosimetry [5] [6] [7].

Various adaptive radiotherapy (ART) techniques have been introduced with the aim of increasing dosimetric accuracy. ART in this context refers to the generation of a new radiotherapy plan based on imaging performed during a patient's treatment course that accounts for the abovementioned changes during treatment. ART with replanning can reduce the doses to OARs and improve patients' quality of life [8] [9] [10] [11] [12]. However, the process of replanning requires additional use of planning equipment and increased staff time.

Several measures for anticipating the need for ART have been described [13]-[21]. There are, however, little published data on optimizing the timing of CT rescanning during treatment.

Recently, deformable image registration (DIR) has been become a very important part of ART [19]. For instance, organ contours have been transferred from the planning CT images to the rescan images using DIR methods such as auto-segmentation [22]-[29]. However, the applicability of DIR in IMRT for HNSCC has been less known and poorly established.

We conducted this study to examine the applicability of DIR in ART and to identify the optical timing of the rescan for replanning.

2. Materials and Methods

2.1. Patient Selection and Clinical Characteristics

Between January 2015 and October 2015, the cases of 22 consecutive patients (17 males and 5 females; median age, 71 years; age range, 44 - 83 years) scheduled to be treated with IMRT for head and neck cancers at our facility were analyzed. This study was approved by the Ethics Committee (approval number: 1631). All patients provided written informed consent to join the prospective cohort study.

Inclusion criteria were histologically-confirmed primary HNSCC; absence of distant metastatic disease; and planned treatment with radical radiotherapy with IMRT technique with or without concurrent chemotherapy. Patients were excluded if they were treated with a three-dimensional conformal radiotherapy technique. Patient demographics, tumor characteristics (including pre-treatment size of the dominant node) and treatment details were recorded on standardized forms. Patient, tumor, and treatment characteristics are shown in Table 1.

Table 1. Clinical characteristics of the two groups.

Characteristics	Replanning group	Non-replanning group	P-value
Number of patients	11	11	
Age (range)	76 (44 - 81)	68 (53 - 83)	0.41
Sex			0.31
Male	7	10	
Female	4	1	
BMI (kg/m^2)	24.4	22.5	0.55
(range)	(17.0 - 28.66)	(15.9 - 28.7)	
Primary tumor site			0.32
Nasopharynx	1	3	
Oropharynx	3	1	
Hypopharynx	3	2	
Larynx	3	1	
Maxillary sinus	0	2	
Ethmoid sinus	0	1	
Nasal cavity	1	0	
Oral tongue	0	1	
Pathological diagnosis			0.33
Squamouscell carcinoma	11	9	
Undifferentiated carcinoma	0	1	
Neuroblastoma	0	1	
Nodal staging			1.00
N0	3	3	
N1	3	3	
N2	5	5	
RT			0.53
Definitive RT	9	10	
Postoperative RT	2	1	
Prescription doses of RT	70 (60 - 70) Gy	70 (60 - 70) Gy	0.17
70 Gy	9	7	
66 Gy	0	3	
60 Gy	2	1	
Chemotherapy			0.11
Carboplatin	1	3	
Docetaxel	3	1	
Cisplatin	1	3	
Cetuximab	4	0	
None	2	4	
Timing of the rescan from the initiation of RT			
Fractions	15 (14 - 19)	15 (13 - 18)	0.69
Days	21 (17 - 30)	20 (17 - 27)	0.91
BMI at rescan (kg/m^2)	23.1	21.3	0.78
(range)	(16.5 - 27.9)	(14.4 - 27.3)	
Weight loss from the initiation of RT to the rescan (%)			
(range)	5.4 (1.7 - 11.2)	4.1 (−3.2 - 9.2)	0.19

Abbreviations: BMI, body mass index; RT, radiotherapy; CT, computed tomography.

2.2. Radiotherapy

All the patients were placed in the supine position and scanned using an Aquilion LB computed tomography (CT) unit (Toshiba, Ohtawara, Japan). The CT dataset was transferred to an XiO treatment planning system (Elekta, Stockholm, Sweden) or MIM Maestro (MIM Software, Inc., Cleveland OH, USA) to outline the volumes of interest (VOIs), and then transferred to a commercial Monte Carlo-based treatment-planning system (TPS), Monaco 2.03 (Elekta, St. Louis, MO, USA).

Intravenous contrast was used for CT scanning in patients with lymphadenopathy. All patients had a positron emission tomography (PET)/CT fused with the planning CT for volume definition. Magnetic resonance imaging (MRI) scans were fused as needed with the planning CT scan to aid in target delineation except for patients receiving adjuvant radiotherapy following surgery. Target volumes were contoured according to the department's standard protocol.

Radiotherapy was designed for VMAT by using a simultaneous integrated boost IMRT (SIB-IMRT) technique in all eligible patients. In patients receiving radiotherapy as their initial treatment, planning target volumes (PTV) were designed as follows: PTV70 received 70 Gy in 2.12 Gy/fraction for gross tumor and metastatic nodes, PTV59.4 received 59.4 Gy in 1.8 Gy/fraction for clinical tumor volumes (CTV) that were considered high-risk, and PTV54 received 54 Gy in 1.64 Gy/fraction for CTVs that were considered as high-risk over 33 days. Treatment regimens and prescription doses are shown in Table 1. The planned radiotherapy was delivered using an Elekta Synergy device (Elekta, Crawley, UK). In addition, daily image guided radiation therapy (IGRT) was performed with cone beam CT. Clinical findings and body weight were recorded once a week. A single radiation oncologist saw all patients and checked and drew all structures. The decision of the need for replanning was made with no consideration of the following analysis.

2.3. Imaging Analysis and Deformable Image Registration

A rescan was planned to be performed at fraction 15 prior to treatment commencement. DIR was performed using a commercial software package, MIM Maestro (MIM Soft-ware, Inc., Cleveland, OH, USA). The process started with a rigid coregistration of the planning CT and the rescan images. Then, the DIR and adaptive contouring module in MIM Maestro (a proprietary intensity-based algorithm) deformed the structures on the planning images to match the rescan images. PTV and OARs including the spinal cord, brain stem, and body outline were analyzed. In addition, the face was analyzed with regard to the volume (whole face) and the face surface (the top 3 mm of skin). The dice similarity coefficient (DSC) was used to evaluate for similarity between the planning CT (A) and the rescan (B), using a scale that ranges from 0 for no correspondence between the images to 1 for complete correspondence. The DSC is defined as follows:

$$DSC = \frac{2 \cdot A \cap B}{|A| + |B|} \quad (1)$$

2.4. Statistical Analysis

We analyzed the weight loss rate and DSC in patients who required replanning (the replanning group) and in patients who did not require replanning (the non-replanning group}. The data are expressed as medians with the ranges in parentheses, unless otherwise indicated. In regards to the association between the two groups, continuous variables and incidence of patients, the trend for incidence was assessed using the Mann-Whitney U-test, the Fisher's exact test and Chi-square test for trend, respectively. The optimal cut-off value was determined using receiver operating characteristic (ROC) curve analysis. All statistical analyses were performed using GraphPad Prism version 6.0b (GraphPad Software Inc., San Diego, CA, USA). A P value < 0.05 was considered statistically significant.

3. Results

The clinical characteristics of the two groups are shown in **Table 1**. No significant differences were observed in the clinical parameters between the two groups. The changes in body weight are shown in **Figure 1**. Not surprisingly, patients' body weights decreased with time. The weight loss rate at rescan is shown in **Figure 2**. No significant differences were observed at rescan. However, the replanning group had weight loss over the duration of radiotherapy and also at rescan. **Table 2** shows the DSC of each structure in the replanning and non-replanning groups. Patients who required replanning showed significantly smaller DSC values in all analyzed structures except for the spinal cord than those who did not require replanning. Based on this data, we focused on the face surface and whole face in the following analysis. The correlation between weight

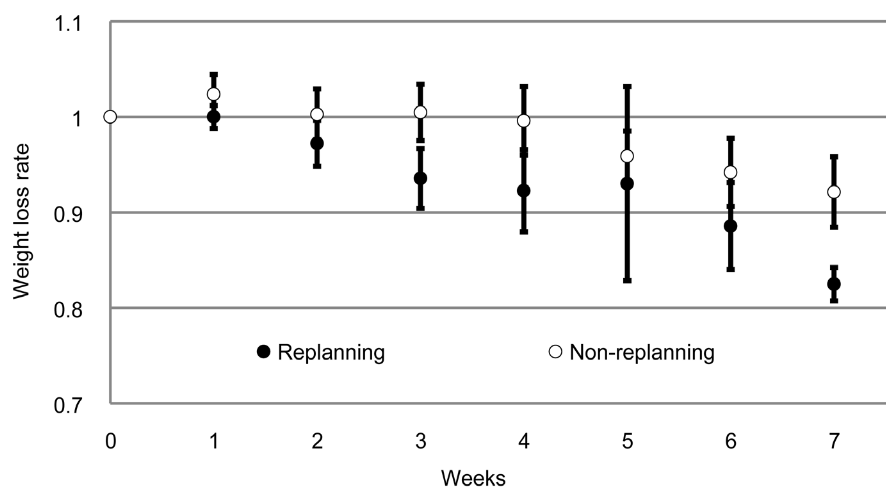

Figure 1. Weight changes in the course of radiotherapy. Patients who needed replanning showed greater weight loss than those who did not. Each point of the two groups is the mean weight loss, and error bars represent one standard deviation.

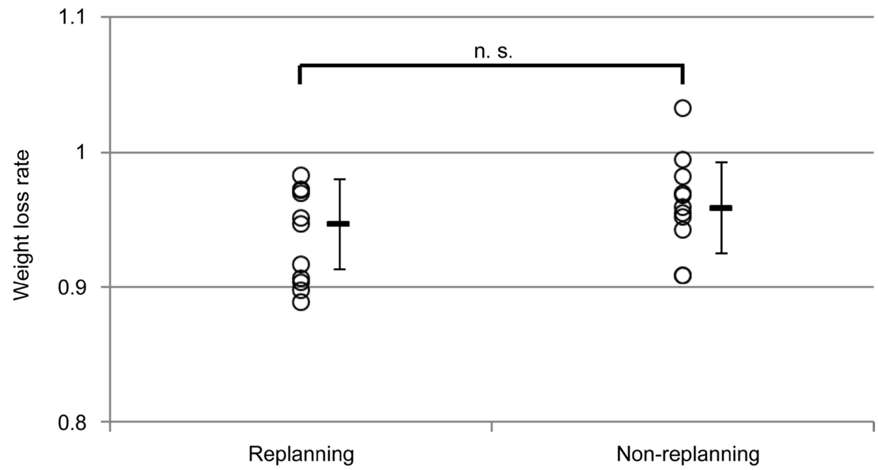

Figure 2. Comparison of weight loss rate between the two groups at rescan. A rescan was planned to be performed at fraction 15 prior to treatment commencement. The weight loss was 5.4% (1.7% - 11.2%) in the replanning group and 4.1% (−3.2% - 9.2%) in the non-replanning group. No significant differences were observed between the two groups (P = 0.19). Median value and standard deviation are placed on the right. n.s.: not significant.

Table 2. DSC of each structure in the replanning and non-replanning groups.

	Replanning group	Non-replanning group	P-value
PTV	0.856	0.928	<0.05
Body	0.964	0.976	0.04
Brainstem	0.855	0.941	0.05
Spinal cord	0.747	0.841	0.07
Face surface	0.420	0.655	<0.001
Whole face	0.960	0.979	<0.01

Abbreviations: DSC, dice similarity coefficient; PTV, planning target volume.

loss and DSC was analyzed (**Figure 3**). There was a significantly negative correlation between the weight loss and DSC in the face surface and whole face. Using the cut-off values of 0.60 and 0.98 for the face surface and whole face, respectively, the replanning group included significantly more patients who developed low DSC values (**Figure 4**).

4. Discussion

IMRT is a well-established standard technique of radiotherapy for HNSCC. SIB-IMRT has the advantages of better target conformity, lower dose to critical structures, moderate treatment acceleration with reduced total treatment time, and the option of dose escalation in the gross tumor volume. In addition, SIB-IMRT can be delivered with a shorter process and save resources compared with conventional sequential boost IMRT. High accuracy is necessary and the same status is ideally required through the treatment duration. However, patients' physical condition can dramatically change over the treatment duration

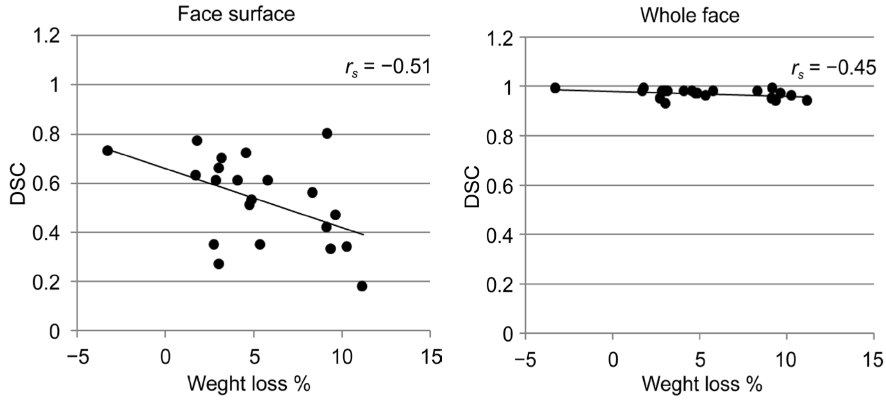

Figure 3. Relationship between weight loss and DSC. Significant negative correlations were observed between the weight loss and DSC in face surface ($r_s = -0.51$, $P < 0.05$) and whole face ($r_s = -0.45$, $P < 0.05$).

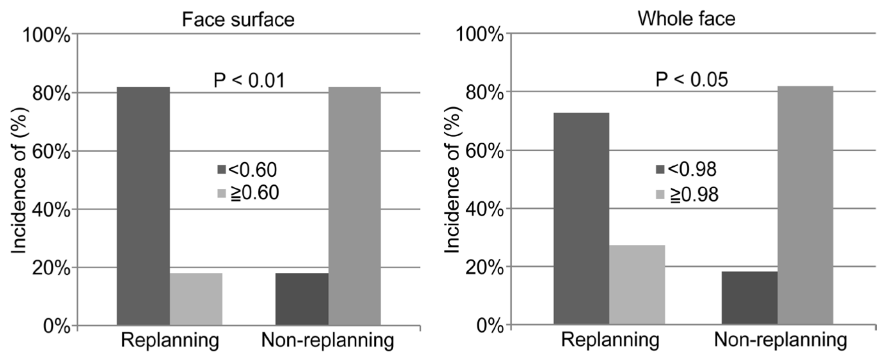

Figure 4. Analysis using the cut-off values in two structures. Compared with the non-replanning group, the replanning group included significantly more patients who developed low DSC values in face surface and whole face ($P < 0.01$, $P < 0.05$, respectively).

because of weight loss and tumor shrinkage. The considerable anatomical changes during the course of radiotherapy may lead to suboptimal dosimetry. Several factors have been reported to predict the need for replanning [8] [9] [13] [14] [15]. However, the optimal timing for replanning is poorly understood.

In the present study, a positive correlation between weight loss and the need for replanning was observed but statistical significance was not reached. Greater weight loss significantly decreased DSC in targets and also OARs. Additionally, patients who needed replanning showed significantly lower DSC values in PTVs including the whole body, whole face, and face surface than those who did not. In addition, ROC analysis revealed the cut-off values of 0.60 and 0.98 for the face surface and whole face, respectively. Using our cut-off values, high DSC values in the face surface and whole face can predict the need for replanning. Therefore, we suggest calculating the DSC of the face surface and whole face in the rescan to assess the need for replanning without manual modifications and subjective evaluation.

The face surface and whole face are relatively large structures whose sizes can improve the sensitivity of replanning. DSC calculations from the rescan can save human resources and time. Greater weight loss predicts the requirement of the modification of structures after auto-segmentation using DIR and that of replanning. We showed that weight loss tended to correlate DSC in a prospective study setting. In this study, the degree of weight loss had insufficiently strong correlation with DSC and the need for replanning. A small sample size might have affected the statistical results. In addition, the head and neck area contain relatively small volumes of fat. It has been reported that body mass index affected the incidence of toxicity in prostate cancer patients [30]. In this study, the clinical findings of toxicity were not mentioned. We expect that further prospective clinical studies with larger numbers of patient would reveal the predictive factors more clearly and the effects of ART and weight loss on anti-tumor effect and toxicity.

Brown *et al.* recently reported a predictive model and the decision tree for ART [13]. However, several parameters such as an initial weight > 100 kg are not applicable to an Asian population and complicate its clinical use. We showed that weight loss could be a simple and valuable parameter to predict the requirement of replanning with manual contouring. Auto-contouring with DIR is a useful tool for ART in clinical practice and can potentially save human resources and time. However, large anatomical changes can cause significant changes in the structures in excess of the adaptivity of the software, leading to errors. Our results indicate weight loss can predict not only the need for replanning but also manually contouring. A further study is needed to show the threshold of weight loss during the duration of radiotherapy and the optimal timing of the rescan for replanning.

We acknowledge that our study has several limitations. Eligible patients had variations in their background characteristics such as differences in primary tumors and delivered radiotherapeutic doses. However, our data was collected prospectively and the focus of our interest was the adequacy of ART with DIR and if weight loss can play a significant role in ART dosimetry. In addition, a single radiation oncologist drew all structures, evaluated the images after DIR, and made decisions on the need for replanning. We therefore believe our data are reliable. In addition, there was no significant difference between weight loss and the requirement for replanning. The sample size was small in this prospective study. However, a tendency of a positive relationship between weight loss and the requirement of replanning was observed. Therefore, based on these data, further prospective data collection might reveal a significant difference and enable the prediction of replanning. Imaging data collected for IGRT during treatment, such as cone beam CT, could also be a useful tool for prediction of replanning [31] [32].

5. Conclusion

DSC that was automatically calculated using CT and DIR technique was a simple and useful parameter to predict the needs for manual contouring and replanning. The cut-off values of DSC were 0.60 and 0.98 for the face surface and whole face, respectively.

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