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Accumulated Dose of Intensity-Modulated Radiotherapy for Head and Neck Cancer Using Deformable Registration of Two Sets of Computed Tomography Images

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Abstract

Purpose: The aim of this study was, using deformable image registration (DIR), to evaluate alteration of dose distribution caused by patient's anatomical structure changes during a two-phase intensity-modulated radiotherapy (IMRT).

Methods: IMRT consisted of an initial plan delivering 53 Gy to gross tumor volume (GTV) and 45 Gy to elective volumes and a boost plan delivering 16.96 Gy to GTV. The subjects were 10 patients with head and neck cancer who underwent computed tomography (CT) scans twice (first CT before treatment and second CT before boost). A sum of the initial and the boost plans for the first CT was Original total plan. Using DIR, the original boost and a modified new boost plan were recalculated on the second CT and summed with the initial plan to create total plans: DIR plan and modified DIR plan.

Results: Mean dose (D_{mean}) of the ipsilateral and contralateral parotids were increased by 8.0% ($P<0.01$) and 6.8% ($P<0.05$) in DIR plan compared with Original total plan. Compared with DIR plan, modified DIR plan reduced D_{mean} of the ipsilateral parotid ($P<0.01$). Dose to 95% of the volume (D95) to clinical target volume for GTV (CTV1) of DIR plan was significantly higher than that of Original total plan ($P<0.01$) and modified DIR plan ($P<0.01$).

Conclusions: Dose summation using DIR demonstrated that the body shrinking during IMRT significantly increased the doses of both parotids and CTV1. Modified DIR plan compensated the increases in doses of the ipsilateral parotid and CTV1.

Keywords: Head and neck cancer; Two-phase intensity-modulated radiotherapy; Anatomic change; Deformable image registration; Replan

Introduction

The attainment of highly conformal dose distribution to targets, while sparing organs at risk (OARs), by intensity-modulated radiotherapy (IMRT) for head and neck cancers (HNC) has recently proved to results in favorable tumor control [1-3]. For HNC patients, radiotherapy inevitably causes weight loss due to reduced dietary intake [4] and the resultant body shrinkage alters dose distribution. In addition, tumor regression and parotid shrinkage during a radiation course reportedly affect dose distribution [5-13]. For conventional radiation therapy, the changes are generally not critical because of the simplicity of dose distribution. For IMRT, on the other hand, these changes cause problems because IMRT dose distributions are highly complicated and conformal. Several studies have reported that dose distribution changes are related to critical alternations of dosimetric parameters for targets and OARs [7-13].

Recalculation based on a series of computed tomography (CT) scans acquired over treatment courses constitutes one solution for this problem. To obtain actual dose distribution of IMRT, however, it is necessary to summate dose distributions based on different CT sets, but this summation cannot be made directly because a given CT set

does not necessarily contain a voxel corresponding to a specific anatomical structure on another CT set. Deformable image registration (DIR) is a method for corresponding the voxel of specific anatomical point on two different CT sets [14,15].

Several studies have compared original dose distributions calculated on single simulation CT with cumulative dose distributions on several simulation CTs using DIR [9-13]. Most of these studies concerned simultaneous integrated boost (SIB) IMRT and demonstrated significant differences between original and cumulative dose distribution. The method used for IMRT at Osaka Medical Center for Cancer and Cardiovascular Diseases is not SIB but a two-phase method in which the initial plan targets both of the gross tumor volume (GTV) and elective volumes and the subsequent boost plan targets GTV exclusively. These two plans are also different in beam directions. These two plans are practically calculated for the first simulation CT (first CT). Compared with the single phase SIB, however, because the two-phase IMRT has these different aspects, the body shrinkage during IMRT could have different influence on dose distributions. To the best of our knowledge, however, no studies on the influence in the two-phase IMRT have been reported. Therefore, in our study, we acquired another simulation CT during the treatment period (second CT) and summated doses of the initial and boost plan using DIR to evaluate the effects of changes in anatomical structures on the dose distribution.

Materials and Methods

Patients

Our study involved 10 patients with HNC who underwent IMRT at Osaka Medical Center for Cancer and Cardiovascular Diseases between July 2011 and September 2012 and was approved by the institutional review board. Written informed consent was obtained from all of the subjects. Table 1 shows patient characteristics.

Characteristics	**No. of patients (n = 10)**
Gender, male/female	10/0
Tumor location	
Nasopharynx	6
Oropharynx	4
Histology	
Squamous cell carcinoma	10
Stage	
T stage (UICC)	
T1	2
T2	5
T3	0
T4	3
N stage (UICC)	
N0	1
N1	2
N2	7
M stage (UICC)	
M0	9
M1	1
Abbreviations: UICC: Union Internationale Contre le Cancer.	

Table 1: Patient characteristics.

Simulation and treatment planning

Treatment planning for first CT

A thermoplastic face mask (CIVCO Medical Solutions, Orange City, IO) was used for patient immobilization during CT simulation and throughout the treatment. The first CT of the head and neck region by GE LightSpeed16 (General Electric Co, Waukesha, WI) was used for all the patients prior IMRT. The CT slice measured 512 × 512 pixels with pixel spacing of 0.977 × 0.977 mm^2 and slice thickness of 2.5 mm. For the simulation CT, points indicating the isocenter were marked on the face mask and simulation CT images were transferred to the Eclipse radiation therapy planning system (ver. 8.9.15; Varian Medical Systems, Palo Alto, CA). Target volumes and OARs were manually contoured by radiation oncologists. In accordance with the recommendations made in reports 50 and 62 by the International Commission on Radiation Units and Measurements [16,17], the primary tumor was included in GTV, which also involved lymph nodes with an axial diameter of at least 10 mm or more. The clinical target volume (CTV) included GTV and surrounding high-risk subclinical disease regions (CTV1) and low-risk subclinical disease regions (CTV2). The planning target volumes (PTV1 and PTV2) were set by adding isotropic 5 mm margins to CTV1 and CTV2, respectively. The spinal cord, brain stem, bilateral parotid glands, oral cavity, mandible, larynx, inferior pharyngeal constrictor, lens, eyes, optic nerves, and chiasm were manually contoured as OARs. Additional safety margins of 5 mm for the spinal cord and 1 mm for the brain stem were used for appropriate planning risk volumes. Intensity-modulated radiotherapy was planned to be delivered with the sliding window method using a 6 MV photon beam of the Varian 23EX linear accelerator equipped with the Millennium 120 multi-leaf collimator (Varian Medical Systems, Palo Alto, CA). For the dose calculation algorithm Analytic Anisotropic Algorithm was used. The radiation treatment consisted of two IMRT plans: 1) an initial plan delivering 53 Gy for PTV1 and 45 Gy for PTV2 concurrently in 25 fractions and 2) a boost plan of 16.96 Gy in 8 fractions exclusively for PTV1 (Table 2). The prescribed doses of the initial and boost plans were normalized to dose to 95% of the volume (D_{95}) of PTV1.

		Dose (Gy)	**Dose (Gy)**
	Fraction	**PTV1**	**PTV2**
Initial plan	25	53	45
Boost plan	8	16.96	-
Total	33	69.96	45

Table 2: Dose allocation for treatment course. Abbreviations: PTV: Planning Target Volume.

First, two IMRT plans were created for the first CT (original initial and original boost plan). The original initial and boost plans were then summed (Original total plan) and OAR doses were assessed based on the RTOG 0615 protocol [18]. The OAR constraints on dose-volume histogram (DVHs) were a maximum dose (D_{max}) of less than 45 Gy for the spinal cord, D_{max} of less than 54 Gy for the brain stem and a mean dose (D_{mean}) of less than 26 Gy for at least one parotid gland. The beam arrangement of the initial plan consisted of seven coplanar beams, typical gantry angles of 50°, 70°, 150°, 180°, 210°, 290° and 310° were used and the boost plan beams were arranged so as to spare the bilateral parotid glands.

Boost plan modification for second CT

The second CT scan with lead balls positioned at the isocenter marks on the face mask was performed around four weeks after the start of treatment. The second CT was registered to the first CT by means of bony anatomy. Organs at risk were newly contoured manually and target volumes for the first CT were copied onto the second CT. To reflect the effect of body changes on dose distribution of the initial plan, the original initial plan was copied onto the second CT and recalculated for the latter half of the initial plan (12 sessions) (recalculated initial plan). Similarly, the original boost plan was recalculated for the second CT (recalculated boost plan). Moreover, for the second CT, the original boost plan was modified mainly to improve the dose volume parameters of the bilateral parotids (modified boost plan).

Calculation of total plan dose based on DIR

Figure 1 shows an overview of the summative dose method using DIR, which was implemented in C++ based on the medical image processing library Insight Segmentation and Registration Toolkit [19]. For the second CT, two registration steps were performed. The first consisted of an affine transformation-based rigid registration performed to remove the setup error between the first CT and second CT. The second registration step was a B-spline-based DIR. This DIR algorithm calculates displacement vector fields (DVFs) corresponding to the anatomic modifications occurring between the first CT and the second CT. The DVFs were used to deform and map the recalculated initial, recalculated boost and modified boost plans of the second CT to create the corresponding deformed plans. On the first CT, these deformed plans were summed up with the original initial plan for 13 sessions to create the total plans, that is, DIR and modified DIR plans (Table 3).

	Initial plan	Boost plan
Original total plan	Original initial plan for 25 sessions	Original boost plan
DIR plan	Original initial plan for 13 sessions + Deformed recalculated initial plan for 12 sessions	Deformed recalculated boost plan
Modified DIR plan	Original initial plan for 13 sessions + Deformed recalculated initial plan for 12 sessions	Deformed modified boost plan
Abbreviations: DIR: deformable image registration.		

Table 3: Planning terms used in this study.

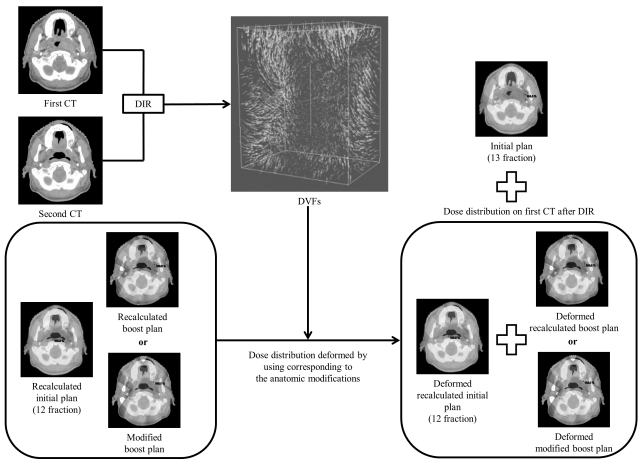

Figure 1: Overview of dose summation with DIR (DVFs displayed with Paraview). Abbreviations: CT: Computed Tomography; DIR: Deformable Image Registration; DVFs: Displacement Vector Fields.

Dosimetric comparison

Original total plan was compared with DIR plan to assess the effect of anatomical changes on dose distribution during treatment. In addition, modified DIR plan was compared with DIR plan to evaluate modification of the boost plan. The dosimetric parameters assessed were D_{95} to CTV1, dose to the maximum of 2% of the volume (D_2) of the spinal cord and brain stem, and D_{mean} to the parotid glands. Beam depth of the original and the recalculated boost plans was compared for quantitative evaluation of changes in body contour during treatment. These comparisons were statistically estimated with the paired t-test. A P value <0.05 was considered significant.

Results

Figure 2 shows the dosimetric parameters of Original total plan, DIR plan, and modified DIR plan. Dose to the maximum of 2% of the volume to the spinal cord of Original total plan, DIR plan, and modified DIR plan were 42.6 ± 2.1 Gy, 43.0 ± 2.1 Gy, and 42.7 ± 2.0 Gy (mean ± SD), respectively, thus showing no significant differences, nor did D2 to the brain stem (47.0 ± 6.1 Gy, 46.8 ± 6.4 Gy, and 46.8 ± 6.1 Gy, respectively).

Mean dose to the ipsilateral parotid of the three plans were 40.0 ± 9.2 Gy, 43.2 ± 9.2 Gy, and 42.6 ± 9.1 Gy (mean ± SD), respectively, showing a significant increase by 8.0% in D_{mean} of DIR plan compared to that of Original total plan (P<0.01), while the difference was slight but significant between the DIR and modified DIR plans (P<0.01). Mean dose to the contralateral parotid of the three plans were 26.4 ± 7.3 Gy, 28.2 ± 7.2 Gy, and 27.8 ± 7.1 Gy (mean ± SD), respectively, showing a significant increase by 6.8% in the Dmean of DIR plan compared to Original total plan (P<0.05), while the difference was not significant between DIR and modified DIR plans (P=0.07).

Dose to 95% of the volume to CTV1 of the three plans were 73.2 ± 0.6 Gy, 73.7 ± 0.8 Gy, and 73.5 ± 0.7 Gy (mean ± SD), respectively, with a slight but significant increase in D95 of DIR plan over Original total plan (P<0.01) and modified DIR plan (P<0.01). Total depth of all

beams was 77.1 ± 14.1 mm (mean ± SD) for the original boost plan for the first CT and 75.0 ± 14.1 mm for the recalculated boost plan for the second CT, with a significant difference between the two plans (P<0.01).

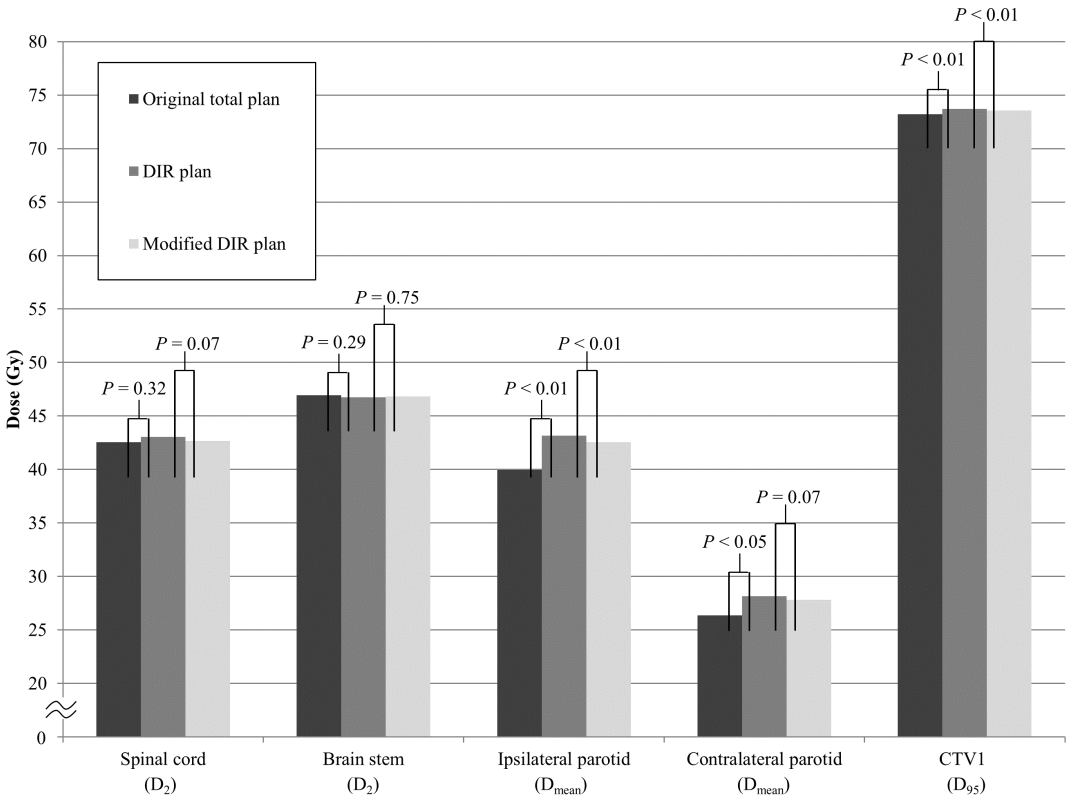

Figure 2: Comparison of dosimetric parameters between Original total plan, DIR plan, and modified DIR plan. Abbreviations: D_2: dose to the maximum 2% of the volume, a representation of maximum dose; D_{mean}: mean dose; CTV: Clinical Target Volume; D_{95}: dose to the 95% of the volume.

Discussion

Several studies of cumulative dosimetric parameters for DIR of repeated CTs during an IMRT course have analyzed the usefulness of DIR for evaluation of alterations in dose volume parameters due to changes in body contours and organ shifts during SIB IMRT. Most of these studies assessed the volumes to the spinal cord, brain stem, parotid glands, and CTV. Table 4 shows a comparison between the doses for Original total plan and DIR plan analyzed in our and previous studies.

Author	No. of Patients	CT during IMRT	IMRT technique	Results			
				Spinal cord (D_2)	Brain stem (D_2)	Parotid (D_{mean})	CTV (D_{95})
Lee et al. [9]	10	Daily	Not stated	Not stated	Not stated	Increase in DIR plan by 3 Gy	Not stated
O' Daniel et al. [10]	11	Twice per week	SIB	Not significant	Not stated	Ipsilateral: Increase in DIR plan by 3 Gy (P = 0.026) Contralateral:	Not significant

						Increase in DIR plan by 1 Gy (P=0.016)	
Wu et al. [11]	11	Six times weekly	SIB	*Not significant	*Not significant	Significant increased	Not significant
Xivry et al. [12]	10	Four times	SIB	Increase in DIR plan by 0.78 Gy	Not stated	Ipsilateral: Increase in DIR plan by 0.93 Gy Contralateral: Increase in DIR plan by 0.53 Gy	Increase in DIR plan by 0.06 Gy
Castadot et al. [13]	10	Four times	Not stated	Difference 0.9 Gy	Not stated	Increase in DIR plan by 0.8 Gy	Not significant
Our study	10	Once	Two-step	Not significant (P=0.32)	Not significant (P=0.29)	Ipsilateral: Increase in DIR plan by 3.2 Gy (P<0.01) Contralateral: Increase in DIR plan by 1.8 Gy (P < 0.05)	Increase in DIR plan by 0.5 Gy (P<0.01)

*Wu et al. used dose to the maximum 1% of the volume of the spinal cord and brain stem. Abbreviations: CT: Computed Tomography; IMRT: Intensity-Modulated Radiotherapy; D_2: dose to the maximum 2% of the volume, a representation of maximum dose; D_{mean}: mean dose; CTV: clinical target volume; D_{95}: dose to the 95% of the volume; DIR: Deformable Image Registration; SIB: Simultaneous Integrated Boost

Table 4: Comparison of the original total plan and DIR plan.

In our study of two-phase IMRT, we could find no differences in D_2 to the spinal cord and brain stem between Original total plan, DIR plan and modified DIR plan. Wu et al. [11] acquired a CT scan every week during an IMRT course for HNC, recalculated the SIB plan for every CT scan and compared the initial plan dosimetric parameters for the first CT with cumulative doses after DIR. Doses to the spinal cord and brain stem were found to be markedly stable. Other studies [10,12,13] reported similar results for comparisons between the initial and cumulative doses to the spinal cord and brain stem. The spinal cord and brain stem are located in the middle of the body and therefore do not shift after body weight loss and/or tumor shrinkage, which is reportedly the reason for the similarity of the doses.

O'Daniel et al. [10] acquired CT scans twice a week during SIB IMRT for HNC, applied the initial plan to the repeated CTs, and produced an integrated plan by using DIR. The median D_{mean} to the ipsilateral and contralateral parotids was higher for the integrated plan than for the original plan by 3.0 Gy (P<0.026) and 1.0 Gy (P<0.016), respectively. They stated that this dose increase was caused not only by setup uncertainty but also by dramatic anatomical changes that occurred over the course of radiotherapy as the patients lost weight, their tumor volume and parotid gland volume shrank, with the center of the parotid gland volume moving medially into the high-dose region. Most other reports [9,11-13] reported that cumulative doses were significantly higher than the dose for the original plan. Our study found that the dose to the parotids for DIR plan was higher than for Original total plan by 8.0% for the ipsilateral and 6.8% for the contralateral parotid. Thus, the results for DIR plans demonstrated that the D_{mean} to the parotids of Original total plan was significantly underestimated, especially to the ipsilateral parotid. We speculate that the primary reason for the dose elevation is the medial shift of the parotids to the higher dose target, and since the ipsilateral parotid is closer to the higher dose region than the contralateral parotid, this would explain why the elevation is more prominent for the ipsilateral parotid.

Xivry et al. [12] acquired CT images 5 times during an IMRT course for HNC and recalculated the SIB plan for each CT set, and cumulated doses for DIR. The therapeutic D_{95} dose to CTV was 68.43 Gy for the actual cumulative dose and 68.37 Gy for the dose of the initial plan. Their study and most other studies [10,11,13] found only minor and insignificant differences in target doses between the actual cumulative doses and those of the original plan. These studies referred to changes in body contour during IMRT, but did not quantitatively assess such changes. The difference in CTV1 D_{95} between DIR plan and Original total plan observed in our study was small and clinically not critical but statistically significant. We measured the beam depth of the original boost plan for the first CT and the recalculated boost plan for the second CT and proved that the total beam depth for the recalculated boost plan significantly decreased probably due to body shrinking. This reduction in depth is thought to be the reason for the higher CTV1 D_{95} of DIR plan.

Table 5 shows a comparison of dose parameters between DIR plan and modified DIR plan of a previous study and our study. Castadot et al. [13] replanned during IMRT, evaluated its effects and found that replanning did not reduce D_{mean} to the parotids. Wu et al. [11] demonstrated that replanning mid-course during SIB-IMRT for HNC efficiently reduced D_{mean} to the parotids by 3 to 6%. Thus, the effect of replanning on parotid dose reduction has been controversial. Neither Castadot et al. [13] nor Wu et al. [11] assessed ipsilateral and contralateral parotid doses separately, our study, on the other hand,

assesses the doses separately and found that, while the contralateral parotid D_{mean} of DIR and modified DIR plans did not differ, the ipsilateral parotid D_{mean} of modified DIR plan was significantly lower than that of DIR plan. Because the ipsilateral parotid may have been closer than the contralateral parotid to the primary tumor and metastatic lymph nodes that were present in the higher dose region and thus shrank during IMRT, the medial shift of the ipsilateral parotid resulted in a more marked elevation of its dose. Modified DIR plan, which compensates for the medial shift, is therefore assumed to be more effective for the ipsilateral parotid.

Author	Results			
	Spinal cord (D_2)	**Brain stem (D_2)**	**Parotid (D_{mean})**	**CTV (D_{95})**
Castadot et al. [13]	Decrease in modified DIR plan by 1.9 Gy	Not stated	Not significant	Decrease in modified DIR plan by 3.1 Gy (target volume modified)
Wu et al. [11]	*Not significant	*Not significant	Decrease in modified DIR plan by 3-6%	Not significant
Our study	Not significant (P=0.07)	Not significant (P=0.75)	Ipsilateral: decrease in modified DIR plan by 1.9 Gy (P<0.01) Contralateral: Not significant (P=0.07)	Decrease in modified DIR plan by 0.2 Gy (P<0.01)

*Wu et al. used dose to the maximum 1% of the volume of the spinal cord and brain stem. Abbreviations: DIR: Deformable Image Registration; D_2: dose to the maximum 2% of the volume, a representation of maximum dose; D_{mean}: mean dose; CTV: Clinical Target Volume; D_{95}: dose to the 95% of the volume.

Table 5: Comparison of DIR plan and modified DIR plan.

In some DIR studies assessing changes in IMRT dose distribution caused by body shrinking, CT scans were acquired repeatedly throughout an IMRT course. A limitation of our study was that we acquired the second CT only once midway through the IMRT course. Hence, anatomical changes after the second CT could not be considered and the differences in dosimetric parameters were relatively small and clinically less significant than those in other studies.

In conclusion, our study for two-phase IMRT clarified that body shrinking during IMRT induced increases in the doses to both parotids and CTV1. New boost plans in our study could compensate the increases in doses of the ipsilateral parotid and CTV1.

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Conflicts of Interest

There are no conflicts of interest.

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