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Feasibility of Margin Reduction for Level II and III Planning Target Volume in Head-and-Neck Image-Guided Radiotherapy – Dosimetric Assessment *via* A Deformable Image Registration Framework

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Abstract: *Purposes:* To improve normal tissue sparing for head-and-neck (H&N) image-guided radiotherapy (IGRT) by employing treatment plans with tighter margins for CTV 2 and 3, and documenting the delivered dose throughout the entire treatment course.

Methods: Ten H&N cases treated with simultaneous integrated boost on a TomoTherapy unit (Accuray Inc.) were analyzed. Dose-limiting critical structures included brainstem, spinal cord, cochleae, parotid glands and mandible. The targets include the PTV1 (gross disease volume), PTV2 (next echelon nodal regions) and PTV3 (areas harboring subclinical disease). The standard margin plans (plan_ref) were generated using the standard margin of 3 mm to CTV1-3. Reduced margin plans (plan_0margin) using the CTV-to-PTV margin of zero for CTV2 and 3 were compared with plan_ref. All patients went through daily pre-treatment mega-voltage CT (MVCT) and weekly kilovoltage CT (kVCT) scans. A GPU-based 3D image deformation/visualization tool was developed to register the weekly kVCT scans with the planning CT scan. The deformation of each contoured structures was computed to account for non-rigid change in the patient setup. Calculation of the dose accumulation was performed to determine the delivered mean/minimum/maximum dose, dose volume histograms (DVHs), etc.

Results: The averaged planned cord maximum doses in Plan_0margin were 7.6% lower, and the parotid mean doses were 18.9% lower than plan_Ref. No significant changes in D_{95} and D_{90} for the CTV2/3 cumulative doses in both reference and Plan_0margin were observed during the planning stage. Under kVCT guidance on TomoTherapy, for the reference plans, the averaged cumulative mean dose ratios during the entire treatment course were consistent within 5% and 1.5% of the planned mean doses for PTVs and CTVs, respectively. Interfraction anatomical changes introduced variations in delivered target doses that reduced the improved normal structure sparing observed in plan_0margin during the planning stage. For the tighter margin plans, the cumulative mean dose ratios were consistent within 4.3% and 2.3% of the planned mean doses for CTV2 and CTV3, respectively. Similar dose variations of the delivered dose were seen for the reference and tighter margin plans. However, the delivered maximum and mean doses for the cord were 20% and 10% higher than the planned doses; a 3.6% higher cumulative mean dose for the parotids was also observed for the delivered dose than the planned doses in both plans.

Conclusions: The GPU-based image framework enables real-time dose verification, accumulation and documentation. By imposing tighter CTV margins for level 2 and 3 targets for H&N irradiation, acceptable cumulative doses were achievable when coupled with weekly kVCT guidance while improving normal structure sparing.

Keywords: Head and neck cancer, CTV-to-PTV margin, image guided radiotherapy, deformable image registration framework.

INTRODUCTION

Radiotherapy has been an effective form to treat head and neck cancer (H&N) in conjunction of chemotherapy. For H&N patients, tumors can be located in the paranasal sinuses, nasal cavity, oral cavity, pharynx and larynx. Since the head

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Table 1. Patient characteristics.

Pt #	Diagnosis	Prescription (Gy)	No. of Fx	Dose/fx (Gy)	Initial Weight (kg)	Weight Change (kg)	Weight Change (%)
1	Tonsil	70	35	2	72.1	-8.8	-12.2
2	BOT*	70	35	2	63.5	-0.9	-1.4
3	Nasopharynx	69.96	33	2.12	81.6	-5.4	-6.6
4	Tonsil	70	35	2	95.7	-10.9	-11.4
5	Tonsil	70	35	2	83.9	-7	-8.3
6	Tonsil	70	35	2	88	-2.1	-2.4
7	Tonsil	70	35	2	93.4	-9.6	-10.3
8	Tonsil	70	35	2	107.5	-11.5	-10.7
9	Tonsil	66	30	2.2	86.4	-4.4	-5.1
10	BOT*	70	35	2	99.8	-10.7	-10.7

*BOT: Base of tongue.

and neck region includes critical structures, the main concern of the treatment is not only an increased survival rate but also protecting the function of these organs [1-5]. State-of-the-art advancements in conformal radiotherapy enabled highly conformal dose distributions that protects the critical structures such as the spinal cord and the parotid glands with the availability of improved dose distributions [6-11].

Undetected and uncompensated factors such as patient posture changes from one treatment fraction to another, and physiological changes such as weight loss or tumor regression may ultimately affect the delivered dose [12-14]. With the advent of image guidance technology, real time imaging was coupled with conformal radiotherapy to form a key tool for quantifying such undetected and uncompensated factors [15-20]. Physicians are able to deliver a planned dose to target more accurately while sparing normal healthy tissue by reducing margins [22-24]. In standard conformal radiation therapy, a 3 to 5 mm margin is given to all the PTVs to compensate for set-up error. However, these safety margins cause an increase in the volume of the high dose region. Since the distance between critical structure and planning target volume decreases during the treatment course, OARs can enter the high dose region. As a result, these organs receive a higher dose than planned [25-26]. Even though a suitable margin has a small effect on dose volume histogram (DVH) and equivalent uniform dose (EUD), tighter treatment margins are necessary when a tumor touches critical structures. It is especially important when such geometric error occurs [12].

In this paper, we performed a study to investigate the feasibility of developing treatment plans with tighter margins to CTV2 and CTV3 as a way to minimize critical structure dose. Specifically, we investigated the feasibility of a 0 mm margin IMRT plan for head and neck tumors. We focused on the normal organ dose at both the planning stage and the delivery stage where patient specific geometric changes occur. The variations in patient geometry were incorporated using a weekly kilovoltage CT imaging. The delivered dose for the 0 mm margin treatment plan was compared with a standard 3 mm margin treatment plan to quantify the amount of critical structure dose that was minimized during the planning and the delivery stages.

MATERIALS AND METHODS

Patient Characteristics

Ten head and neck cancer patients treated with a simultaneous integrated boost IMRT technique on a TomoTherapy unit (Accuray Inc., Sunnyvale, CA) were considered in this work. Table **1** shows patient characteristics for the patients included in this study. All patients received daily pre-

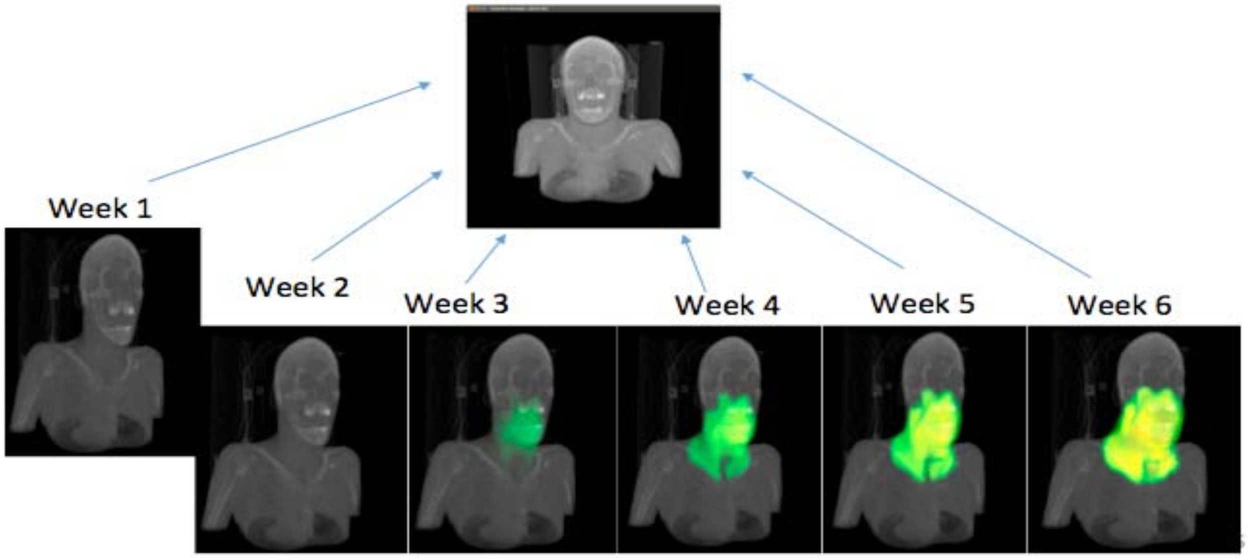

Fig. (1). A schematic illustration of the dose accumulation using the weekly CT scan.

treatment MVCT scans and weekly kVCT scans during the course of treatment. The planning kVCT images were acquired on a Philips Brilliance CT system (Philips Medical Systems, Best, The Netherlands). All patient kVCT images were acquired with the patient in the simulated treatment position with a 50-70 cm FOV, 512x512 in-plane resolution, and a 3 mm slice thickness. In total, 71 weekly kVCT scans were analyzed. The patients' weight was recorded weekly during the treatment course.

IMRT Treatment Planning on TomoTherapy

The clinical tumor volumes (CTVs) were delineated on the planning CT by adhering to the principle of respecting anatomic boundaries. CTV1 was defined as any visible tumor mass as delineated on imaging studies, whether at the primary site or cervical lymphatics. It often coincided with the gross tumor volume (GTV) plus the perceived direct disease extension, and may encompass the entire anatomic structure (such as the nasopharynx) to which the treating radiation oncologist feels necessary to deliver tumoricidal dosage sufficient for controlling a bulky tumor (traditionally held to be around 70 Gy in 2-Gy per fraction scheme). CTV2 was defined as either an adjacent area or structure perceived to be at risk, or the next echelon lymphatic drainage areas. For post-resection cases, it also included surgical bed where a somewhat moderate level of dosage (*e.g.* 60 Gy) may be needed in order to compensate for the perceived accelerated repopulation of residual tumor cells. Finally, CTV3 is defined as any target volume which may harbor only subclinical (*i.e.* undetectable clinically) disease such as micrometastases, for which a relatively low dose level (*e.g.* 50 Gy) might be sufficient. In general, these CTV structures are determined based on each individual physician's practicing philosophy with respect to the tumor's perceived anatomic extent. The critical structures including brainstem, spinal cord, cochleae, parotids, mandible, etc were also delineated. Two IMRT plans were created using different CTV-to-PTV margin. For the standard plan, a CTV-to-PTV margin of 3 mm was given for PTV1-3 (plan_ref); a reduced margin plan (plan_0margin) was created using 3 mm margin for PTV1 while zero margins were employed for CTV2 and 3. The prescription doses were in the range of 50-70 Gy in 30-36 fractions for PTV1 (gross disease volume), PTV2 (next echelon nodal regions) and PTV3 (areas harboring subclinical disease). Before each treatment, alignment was performed using in-room lasers and 3-point markers on the patient with the customized immobilization device.

For all cases, all treatment plans were created on the TomoTherapy planning system (version 4.0) using the following parameters: field width of 2.5 cm, modulation factor of 2.5 and pitch of 0.287.

In-house Deformable Image Registration (DIR) Framework

Tracking anatomical changes is crucial to account for geometric changes in the patient anatomy [27-28]. We employed an in-house GPU-based dense optical flow registration algorithm for registering planning kVCT with the weekly kVCT scan [21]. We considered the weekly kVCT scan as the target 3D image and the planning kVCT as the source 3D image.

The DICOM objects for each patient, including treatment planning CT, planning CT structure set, planning dose and the weekly kVCT images were exported to an in-house DIR framework.

As a first step, the source/target pair was resampled to have the same image dimensions and resolutions. A multi-resolution registration approach was used to account for voxel displacement greater than 1 voxel distance. The number of resolution levels and the smoothness values were set to 5 and 150 as they provided optimal registration to account for non-rigid geometric continuity. The registration process computed the displacement vectors associated with each voxel in the planning kVCT scan. The treatment plan corresponding to the planning kVCT scan was finally warped to compute the dose to be delivered that corresponded with the weekly kVCT scan. Finally, the doses to be delivered to critical structures were recomputed. Fig. (**1**) shows a schematic illustration of the dose accumulation using the weekly CT scan. The dose to be delivered. It can be seen that at the end of the treatment fractions, the dose delivered for the critical structures and the tumor was documented for each voxel.

Dose Accumulation for the Reduced Margin Plan

To simulate the delivered dose and cumulative dose for the reduced margin plan, we used the weekly kVCT scans acquired for the standard margin plan at treatment position. Each pretreatment weekly kVCT was registered using our in-house DIR framework and deformed to the corresponding planning CT scan. The deformed new structure set (with zero expansions of CTV-to-PTV for level II and III) representing the anatomy on a given treatment fraction populated from the planning CT. The delivered dose distributions based on plan_0margin for the targets and critical structures were computed and compared with the plan_ref.

RESULTS

In this section, we first present our results on comparing the treatment plans developed with zero margins for CTV2 and CTV3 with the treatment plans developed using conventional margins. We then present our results on comparing the delivered dose for both the CTVs and the critical structures using the two planning strategies. Ten head-and-neck cases were analyzed and presented in this work. The DVHs of the standard plan (plan_ref) and the reduced margin plan (plan_0margin), and the actual accumulated doses for both plans were calculated and compared.

Dosimetric Comparison of the Standard Plan Versus the Reduced Margin Plan

Fig. (**2**) shows the dose distribution of the standard margin plan (top) versus the reduced margin plan (bottom) for a representative case (patient 5). The DVHs of the selected structures for the same case are displayed in (Fig. **3**). For both the standard plan and the reduced margin plan, the PTV1 remains sufficient coverage, the CTV2 and CTV3 shows no significant difference, while great OAR sparing for the cord, the brainstem, left- and right-parotid glands are clearly seen in the reduced margin plan. The detailed planned dose metrics, such as maximum cord dose, mean doses of the left- and right- parotid glands, the maximum and average doses for the PTV1, CTV2 and CTV3 of both standard and the reduced margin plans are tabulated in Table **2**.

Fig. (**4**) shows the ratios of the selected dosimetric parameters for the reduced margin plans and the standard margin plans. It appears that the mean doses for CTV2 and 3 are consistent within 3% and 4.9% respectively between the plans with and without margin. However, large variations (up to 45%) of parotid gland mean dose sparing was seen for patient #1 and #5 for zero margin plan; up to 30% of the cord max dose was observed compared to the standard margin plan. Student t-test was performed for the dosimetric parameters between the standard margin versus reduced margin plans, the p-values are 0.01, 0.40, and 0.38 for the maximum cord, mean left-parotid and right-parotid glands respectively. For the targets, com-

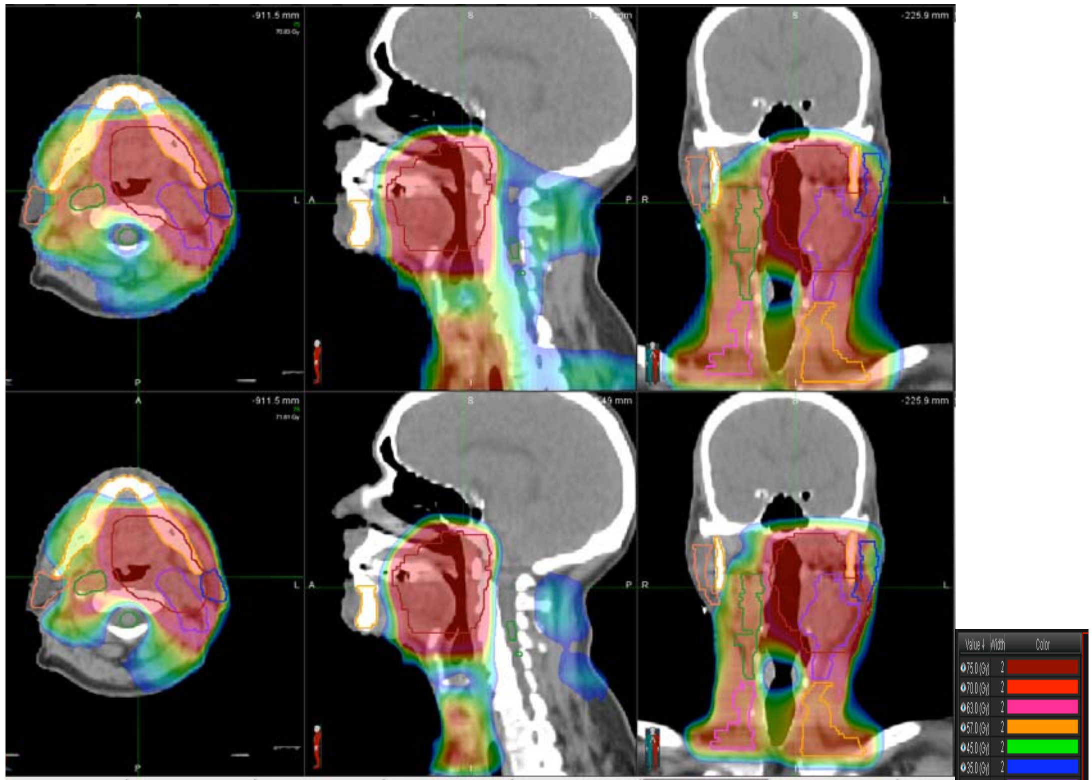

Fig. (2). Dose distribution on a transverse, sagittal and cornel view of the plan_ref and the plan_0margin for a representative case (patient #5).

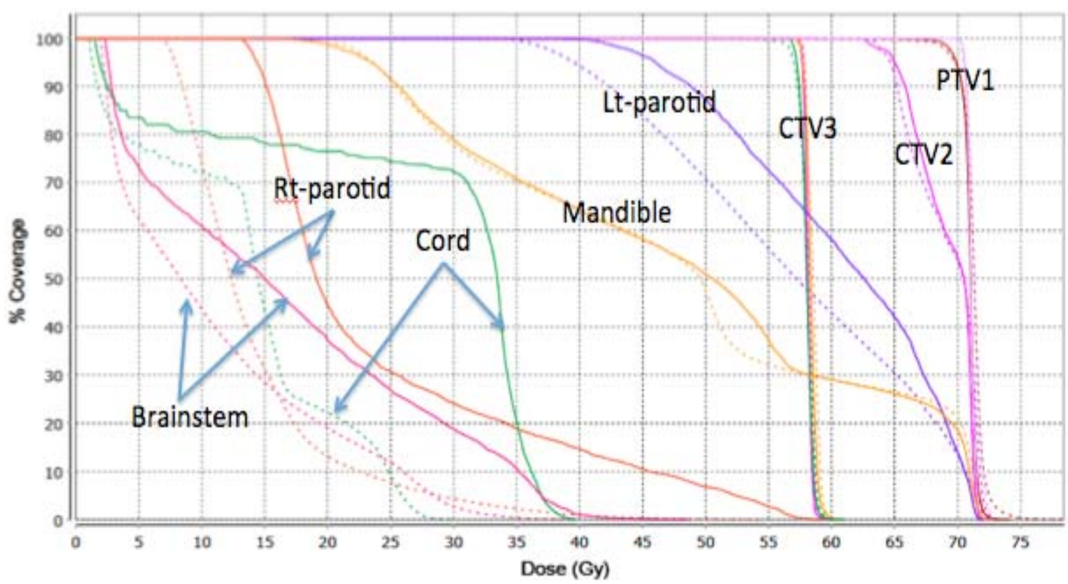

Fig. (3). DVH comparison of the standard plan (solid line) versus the reduced margin plan (dotted line) for patient 5.

parable doses were found for all PTV1, CTV2 and CTV3. Such observations support the fact that treatment plans with zero margins for CTV2 and CTV3 facilitate a treatment that delivers the same dose to the tumor volume as that of a conventional treatment plan while dramatically reducing the dose delivered to organ-at-risks.

Delivered Cumulative Dose Comparison

Each pre-treatment image was acquired to ensure the correct patient alignment and thus the delivered dose distribution to match with the planned dose distribution. Fig. (**5**) displays the comparison of the actual delivered dose for the parotid glands between the standard margin plan and the reduced

Table 2. Dosimetric Parameters Between the Standard Margin Versus the Reduced Margin Plans.

Pt #	PTV1		CTV2		CTV3		Cord	Lt-Parotid	Rt-Parotid
	Max Dose (Gy)	Ave Dose (Gy)	Max Dose (Gy)	Ave Dose (Gy)	Max Dose (Gy)	Ave Dose (Gy)	Max Dose (Gy)	Ave Dose (Gy)	Ave Dose (Gy)
	Standard Margin Plan								
1	76.69	71.83	74.43	72.25	74.0	72.29	41.51	22.4	38.88
2	74.39	71.01	73.36	71.82	72.4	67.67	41.83	24.02	61.41
3	74.45	71.37	73.55	66.05	72.9	66.99	33.22	56.42	49.19
4	74.22	72.07	73.7	70.39	62.36	57.71	44.91	62.98	23.37
5	74.11	70.99	72.92	71.07	72.68	69.22	39.65	60.93	24.55
6	77.93	71.13	75.03	68.02	70.90	64.23	39.63	24.85	24.56
7	73.99	71.43	73.99	71.7	73.48	67.7	43.39	40.98	14.02
8	76.47	71.56	76.47	69.05	73.3	59.13	44.32	27.48	22.92
9	69.33	67.31	68.93	66.61	68.93	58.91	42.71	7.56	38.83
10	74.16	71.14	73.01	67.02	72.12	61.99	40.18	22.76	20.81
Mean	74.54	70.97	73.51	69.62	71.12	65.44	41.00	29.84	29.06
	Reduced Margin Plan								
1	74.65	71.68	72.46	70.11	71.78	68.75	38.11	19.55	29.35
2	74.61	71.35	72.80	69.79	73.06	67.15	29.06	13.09	59.03
3	73.57	69.85	72.81	67.06	71.27	65.16	27.77	51.34	48.92
4	75.45	72.48	75.06	70.38	61.59	57.81	34.7	58.71	19.37
5	78.26	71.27	72.03	68.98	73.25	69.2	29.35	57.01	14.14
6	76.38	70.9	77.55	67.79	69.83	63.91	36.73	21.03	19.90
7	76.21	71.35	73.96	71.24	72.35	66.81	38.68	40.83	12.72
8	77.0	71.86	76.76	69.11	73.96	59.1	41.24	26.52	21.16
9	71.6	67.84	70.31	66.77	69.95	59.15	43.89	6.87	37.68
10	73.87	71.43	73.48	66.93	72.56	62.04	39.53	21.24	12.85
Mean	75.13	70.99	73.69	68.79	70.87	63.78	35.50	26.08	23.87

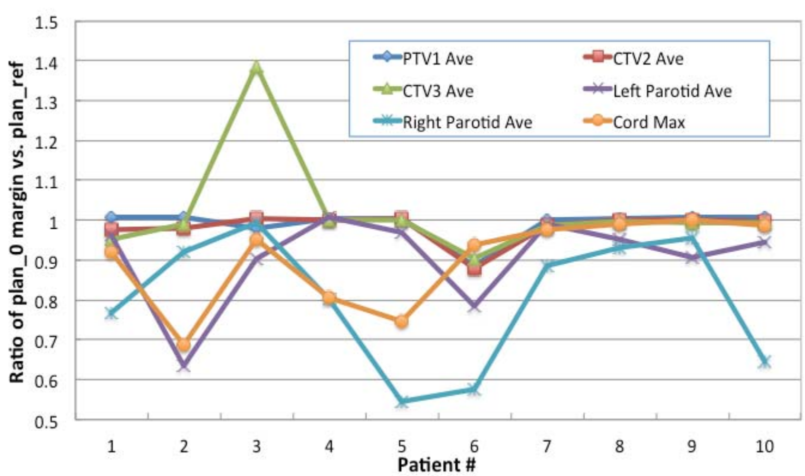

Fig. (4). The ratios of the dosimetric metrics between the plan_0margin and plan_ref for the targets and the selected structures.

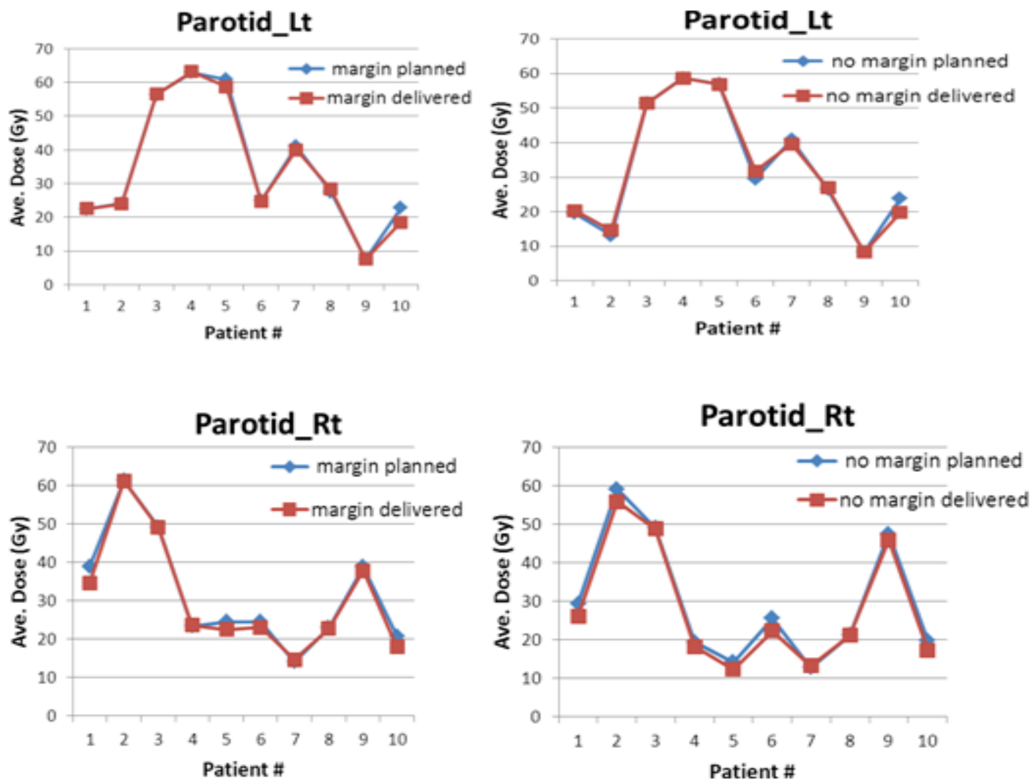

Fig. (5). Comparison of the actual delivered dose for the parotid glands between the standard margin plan and the reduced margin plans.

margin plans for the group of 10 cases. The delivered dose, in general, agreed well with the planned doses for both standard margin and reduced margin plans. For the cord maximum dose, left-parotid mean dose and right-parotid mean dose, the planned dose versus the delivered dose are p=0.19 (the standard margin) *vs.* 0.31 (the tighter margin); p=0.45 (the standard margin) *vs.* 0.44 (the reduced margin); p=0.43 (the standard margin) *vs.* 044 (the reduced margin), respectively. Between the delivered doses with the standard margin versus no margin, the p=0.16, 0.45 and 0.49 respectively. By the end of the treatment course, all clinical target volumes received the acceptable doses as was expected.

The accumulated dose was checked for all patients to evaluate how closely the planned dose distribution was followed. Since kilovoltage computed tomography was used for dose calculation, each weekly dose was corrected based on a fraction in order to compare the two following weeks. Based on this comparison. The weekly accumulated dose given to the patients is similar equivalent to the weekly planned dose. Moreover, the total delivered dose is the same as with the planned dose. As a result, tumor coverage was provided with the zero margin plans.

Validation of the In-house Deformation Framework

The accuracy and the robustness of the analysis were greatly dependent on the accuracy of the in-house registration algorithm (28). We validated the head and neck registration using a landmark-based Target Registration Error (TRE) metric [30]. For our analysis, we considered the planning kVCT to be source 3D image and the kVCT of the last week of treatment to be the target 3D image. A set of 80 landmarks was marked on the rigid structures of a reference kVCT and tracked from one kVCT dataset to another. Fig. (**6**) presents the user interface that we employed for our validation process. The landmarks were placed by an expert on the reference kVCT data (left) as shown by the cross hairs. For each of the landmarks, the corresponding landmark in the target kVCT data was calculated using the image registration results and were visually shown to the expert as cross hairs overlapping the target (right) image. Based on the results, the expert either accepted the registration results or marked the correct landmark on the tar-

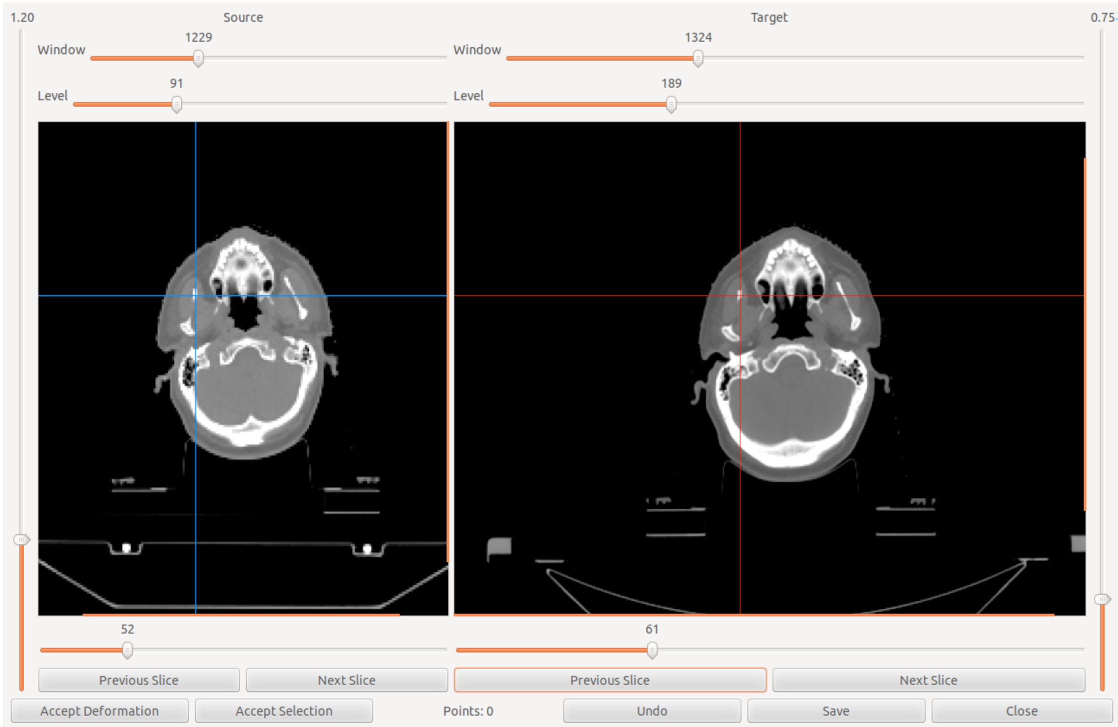

Fig. (6). The user interface developed for performing a landmark based head and neck registration validation.

Table 3. Landmark based validation of the in-house registration algorithm.

Patient	TRE (mm)
1	0.72
2	0.65
3	0.94
4	1.3
5	1.4
6	1.1
7	0.9
8	0.8
9	0.9
10	0.7

get image. Once the 80 landmarks were delivered, the TRE for each of the datasets were computed. Table **3** tabulates the DIR registration results for the group of ten cases. For each of the datasets, the TRE was found to be in the range of 0.5-1.13 mm.

DISCUSSION

One of the major challenges of the IMRT treatment is to minimize doses to the critical structures while providing the intended dose to the target. To ensure sufficient target coverage, the common practice is imposing a proper margin to the planning target volume from the clinical tumor volume to account for uncertainties in planning or treatment delivery [29]. The PTV is meant to encompass beyond CTVs by compensating for patient set-up and motion uncertainties, which may take on a random (Gaussian) orientation 3-dimensionally. Such CTV-to-PTV margin is thus driven by the practicing physics protocol, and may be modified based on the existing patient setup-motion compensation technology such as image-guided radiation therapy (IGRT). With IGRT, we aim to better spare the OARs by further reduction in such CTV-to-PTV margins, in particular for CTV2 to PTV2 and CTV3 to PTV3 expansions. As for PTV1, we feel that adequate margins beyond CTV1 should still be preserved despite image-guidance endeavor, since the outlining of CTV1s by physicians already entails certain degree of educated guess such that any systemic reduction of the perceived gross tumor extent by physics protocol could translate into significant compromise in the ultimate tumor control probability. It is known that PTV is a geometric concept that takes into consideration the net effect of all possible geometric variations and is used to ensure that the CTV receives the prescribed dose.

These geometric uncertainties include organ delineation, setup errors, and organ motion that occur throughout the planning and treatment process. The clinical implementation of margin reduction may also depend on the patient immobilization devices, the image quality [31], IGRT procedures, the anatomic sites, etc. [32].

Stroom *et al.* [33] and van Herk *et al.* [34] derived CTV-to-PTV margin recipes accounting for the systematic and random setup errors. An important shortcoming of these margin recipes is their lack of adequately incorporating both rotational and morphologic errors [35]. In this study, we used a novel approach to assess the feasibility of margin reduction *via* a GPU-based framework. Through a retrospective study of real IGRT images, we simulated the daily and cumulative dose distribution if reduced margins for CTV II and III were imposed when patients were in the actual treatment position. With image guidance, the dose distribution based on the reduced margin plans appeared to be acceptable for the CTV2 and 3; in the meantime, better OAR sparing, compared with the standard margin plan, would be possible. For the patients who had large anatomic changes, such as target shrinkage, weight loss, etc during the course of the treatment, an adaptive plan based on the new anatomic could be considered.

The reproducibility of patient setup is of particular importance for head and neck IMRT treatment due to the proximity of targets to the critical structures and the sharp dose falloff of the planned dose distribution. The standard patient immobilization device for head and neck irradiation is a customized head and neck thermoplastic masks. However, the head and neck mask may not provide sufficient immobilization of the shoulders, which is of importance in comprehensive nodal irradiation in the neck area. The reduction of CTV2 and CTV3 margin calls for better patient immobilization devices, such as the head and neck shoulder mask or better robust patient alignment procedure, to provide better immobilization of the entire upper part of the body in the treatment position. Clinical validation is needed to verify the immobilization accuracy of the device. Caution needs to be taken when tightening the CTV-to-PTV margin in clinical practice.

In addition, the CTV-to-PTV margin of head-and-neck cancer may be affected by the imaging modality. Various IGRT modalities, such as KV cone beam CT (KVCBCT), mega voltage cone beam CT (MVCBCT), mega voltage fan beam CT (MVCT) are available and widely used in clinical practice. The image quality obtained from these on-board CT systems is not as good as the planning kVCT. As a result, large margin may be necessary for the on-board image systems with inferior image quality due to large random error [31].

CONCLUSION

We presented a feasibility study of potential margin reduction for Level II and III planning target volumes in image-guided H&N radiotherapy. An in-house GPU-based deformable image registration framework was used to compute the delivered dose based on weekly images and the delivered accumulative dose during the entire course. Reduce CTV-to-PTV expansion for level II and III targets for H&N irradiation may greatly reduced the dose delivered to the critical structures, such as the parotid glands and cord. However, it was observed that subject-specific anatomical changes led to a higher dose delivered to critical structures. Thus, while using tighter margins for the CTV2 and CTV3 may lead to better sparing of normal tissues, adaptive re-planning will be required in order to account for changes in the patient geometry. The kVCT guidance with zero CTV-to-PTV margin appears to result in acceptable cumulative doses to the targets (CTV2 and CTV3) while greatly improving normal structure sparing.

Future work would focus on developing adaptive radiotherapy strategies for head and neck radiotherapy that will ensure zero margin treatment plans are delivered accounting for changes in the patient geometry. Advancements in image registration and biomechanical head and neck modeling will lead to a precise tracking of patient anatomy changes from one treatment fraction to another. Such adaptive radiotherapy strategies will eventually lead to a better sparing of normal organs and to a better patient quality of life. Future work would also include a systematic analysis of random errors that will have to be included in the zero-margin treatment plans and their impact on the dose improvements. Such a study would be critical to document the need the for algorithm improvements in image registration and biomechanical modeling as a way to minimize the impact of random errors on the dosimetric improvements provided by the zero-margin treatment plans.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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