Measuring uncertainty in dose delivered to the cochlea due to setup error during external beam treatment of patients with cancer of the head and neck

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Purpose: To use Cone Beam CT scans obtained just prior to treatments of head and neck cancer patients to measure the setup error and cumulative dose uncertainty of the cochlea.

Methods: Data from 10 head and neck patients with 10 planning CTs and 52 Cone Beam CTs taken at time of treatment were used in this study. Patients were treated with conventional fractionation using an IMRT dose painting technique, most with 33 fractions. Weekly radiographic imaging was used to correct the patient setup. The authors used rigid registration of the planning CT and Cone Beam CT scans to find the translational and rotational setup errors, and the spatial setup errors of the cochlea. The planning CT was rotated and translated such that the cochlea positions match those seen in the cone beam scans, cochlea doses were recalculated and fractional doses accumulated. Uncertainties in the positions and cumulative doses of the cochlea were calculated with and without setup adjustments from radiographic imaging.

Results: The mean setup error of the cochlea was 0.04 ± 0.33 or 0.06 ± 0.43 cm for RL, 0.09 ± 0.27 or 0.07 ± 0.48 cm for AP, and 0.00 ± 0.21 or -0.24 ± 0.45 cm for SI with and without radiographic imaging, respectively. Setup with radiographic imaging reduced the standard deviation of the setup error by roughly 1–2 mm. The uncertainty of the cochlea dose depends on the treatment plan and the relative positions of the cochlea and target volumes. Combining results for the left and right cochlea, the authors found the accumulated uncertainty of the cochlea dose per fraction was 4.82 (0.39–16.8) cGy, or 10.1 (0.8–32.4) cGy, with and without radiographic imaging, respectively; the percentage uncertainties relative to the planned doses were 4.32% (0.28%–9.06%) and 10.2% (0.7%–63.6%), respectively.

Conclusions: Patient setup error introduces uncertainty in the position of the cochlea during radiation treatment. With the assistance of radiographic imaging during setup, the standard deviation of setup error reduced by 31%, 42%, and 54% in RL, AP, and SI direction, respectively, and consequently, the uncertainty of the mean dose to cochlea reduced more than 50%. The authors estimate that the effects of these uncertainties on the probability of hearing loss for an individual patient could be as large as 10%. © 2013 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4830427>]

Key words: setup error, dose uncertainty, cochlea, head and neck

1. INTRODUCTION

Head and neck cancer patients treated with Cisplatin-based chemotherapy and external beam radiotherapy may develop sensorineural hearing loss (SNHL).¹ Recent QUANTEC studies estimate the relationship between SNHL and the radiation dose delivered to the cochlea.² However, the effects of uncertainty of the cochlea dose have not been included in these studies.^{3–7} As an initial step toward understanding these effects on dose response models for hearing loss, we study the uncertainty in dose to the cochlea during head and neck cancer treatments.

The cochlea is a spiral-shaped bony structure in the inner ear cavity rigidly connected to the skull, and cochlea's organ deformation is not significant. Therefore, the motion of the cochlea can be assumed to be rigid and described by three translational and three rotational degrees of freedom. Since intrafractional motion of the skull is minimal in patients set

up with face masks, the uncertainty in cochlea dose mainly results from the rigid displacements and rotations caused by interfractional setup error.⁸

At Memorial Sloan-Kettering Cancer Center (MSKCC), head and neck patients are treated using weekly KV imaging to correct patient setup, and similar procedures are common at other institutions. The overall uncertainties in position and dose resulting from this procedure are an admixture of those from days with imaging, and those without. Our purpose in this paper is to study the dosimetric and positional uncertainties for the cochlea introduced by typical setup inaccuracy, and to quantify the reduction in these uncertainties resulting from image-guided setup.

Head and neck cancer patients treated with IMRT at MSKCC received weekly KV radiographic imaging to verify and correct patient setups. On these days, after having been setup with KV radiographic image pairs, all patients studied in this paper also received Cone Beam CT (CBCT) scans

TABLE I. Disease sites of ten patients in this study. The total number of CBCT images is 52. Prescribed dose is those of the PTVs using dose painting.

Patient	Cancer site	Fractions	Prescription doses	Number of CBCTs
			(cGy, PTV1, PTV2, PTV3)	
1	Oropharynx	33	5940, 7000	4
2	Nasopharynx	33	5940, 7000	7
3	Oropharynx	33	5412, 5940, 7000	5
4	Mandible	20	4400	4
5	Oropharynx	33	5412, 5940, 7000	5
6	Nasopharynx	33	5610, 5940, 7000	4
7	Neck	35	6300, 7000, 8000	6
8	Hypopharynx	33	5410, 5940, 7000	6
9	Nasopharynx	33	5940, 7000	5
10	Nasal sinus	33	5412, 5940, 7000	6

to record their positions at the treatment. The couch shifts associated with each pair of KV radiographic images were stored in Varian's ARIA (Ref. 9) database and were used to reconstruct the position of the cochlea both with and without the image-guided setup correction. In this paper, we register the cochlea in the CBCT to those in the planning CT, and determine the cochlea's translational and rotational setup errors at treatment, with or without the KV radiograph-based couch shift. The registrations are used to calculate the treatment doses to the cochlea for each fraction and to accumulate these doses after each fraction. The dose uncertainties to the cochlea and their relationship to the setup errors are also discussed.

2. MATERIALS AND METHODS

Thirteen head and neck cancer patients treated with external beam IMRT at MSKCC from 2004 to 2009 received a weekly cone beam scan at time of treatment on the same day as KV radiographic images were taken, as part of a setup error study using the Varian On-Board Imager system on the Varian 21EX linear accelerator (Varian Medical Systems, Palo Alto, CA). Three of those patients were excluded from our study because records of shifts of couch positions were not found. In addition, only CBCT scans covering the cochlea were selected. We have a total 10 planning CT and 52 CBCT scans used in this study.

For head and neck patients treated at MSKCC, dose is usually delivered in 33 fractions and prescribed to two or three levels using dose painting as follows: Dose to PTV70, based on gross disease, is 7000 cGy, dose to PTV59, based on high risk subclinical regions, is 5940 cGy, and dose to PTV54, based on low risk regions, is 5412 cGy. The treatment details, prescription doses and number of cone beams scans for the study patients are listed in Table I. The disease sites vary from nasal sinus, mandible, neck, tonsil, nasopharynx, hypopharynx, and the base of tongue.

The patients received five treatment fractions per week, and every fifth treatment the setup was corrected in an imaging session, during which orthogonal KV radiographs, and for patients in our study, a CBCT, were obtained. The CBCT scan was performed after the patient had been setup with KV radiographs and was not used to adjust patient setup. Our analysis of cochlea setup and dosimetric errors using the CBCT data was performed after all treatments were delivered, and did not affect treatment in any way. Figure 1 shows the flow chart of setup procedure for the patients in this study, on imaging and nonimaging days. For the initial setup, the patient is first positioned with the room lasers and body tattoos, followed by any couch shift determined on the previous imaging day. On imaging days, a further couch shift is determined by registering bony landmarks seen in KV radiographs to those in the digitally reconstructed radiographs generated from the planning CT. As is standard practice at our institution, the correction determined during

FIG. 1. Setup procedure for the head and neck patients under study on imaging and nonimaging days (top and bottom, respectively). Initial setups incorporate the couch correction from the previous weeks imaging session. *Initial setup: Setup to tattoos plus the shift for setup error from the previous imaging session.

each imaging session was applied until the next imaging session.

Records of the couch shifts performed to correct the initial setup, together with the CBCT, enables us to reconstruct the setup errors of both the initial and the radiograph corrected setup. Since the initial setup of the patient on imaging days is the same as the procedure used on nonimaging days, we assume that the distribution of uncertainties in cochlea position from the initial setups represent those present on days when no images were taken. We emphasize that in what follows, the setup and dose uncertainties are all calculated from data taken on imaging days.

To estimate the uncertainties in cochlear dose delivered on treatment days in which imaging either was or was not performed, we developed the following method which allowed all dose calculations to be done on the planning CT data set. A coordinate system [x(RL), y(AP), and z(SI)], with its origin at the center of each CT data set was defined. Automatic, rigid image registration incorporating both translation and rotation, followed by manual adjustment, was used to register each CBCT to the planning CT based on a volume of interest around the cochlea. After registration, a point (x_0, y_0, z_0) in the CBCT and the corresponding point (x, y, z) in the planning CT are related by the following transformation:

$$\begin{pmatrix} x \\ y \\ z \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \cos \vartheta_x & -\sin \vartheta_x \\ 0 & \sin \vartheta_x & \cos \vartheta_x \end{pmatrix} \begin{pmatrix} \cos \vartheta_y & 0 & \sin \vartheta_y \\ 0 & 1 & 0 \\ -\sin \vartheta_y & 0 & \cos \vartheta_y \end{pmatrix} \times \begin{pmatrix} \cos \vartheta_z & -\sin \vartheta_z & 0 \\ \sin \vartheta_z & \cos \vartheta_z & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} x_0 + \Delta x + dx \\ y_0 + \Delta y + dy \\ z_0 + \Delta z + dz \end{pmatrix}. \quad (1)$$

In Eq. (1), $(\Delta x, \Delta y, \Delta z)$ is the translation and $(\vartheta_x, \vartheta_y, \vartheta_z)$ is the rotation of the CBCT with respect to the planning CT, and (dx, dy, dz) is the couch shift based on the KV radiograph after patient setup. Thus, after registration of the cochlea in the planning CT with those in the CBCT, we can calculate the residual setup error of the cochlea after KV based radiographic setup. Setup errors of the initial setup may be calculated by taking the KV based correction (dx, dy, dz) to be $(0, 0, 0)$. We assume that the distribution of setup errors from these initial setups may be taken to represent those present on days when KV based imaging is not performed. In what follows, we refer to the setup errors and dose uncertainties of the cochlea, using either the initial or KV corrected setups, as either “without KV radiograph correction” or “with KV radiograph correction,” respectively. Set-up errors found by this method are not impacted by geometrical off-sets between the CBCT, kV radiographic imaging systems or the treatment isocenter, since standard QA of these devices has shown these offsets to be less than 0.4 mm.

Due to the small volume and rigid motion of the cochlea, we used the geometric Center of Gravity (COG) point within each cochlea volume to represent the position of the cochlea. The cochlea setup error at each imaging session is then defined as the difference between the cochlea COG position in the planning CT, calculated either with or without that session’s registration transformation applied.

In order to calculate the dose delivered to the cochlea with or without KV radiographic imaging-based correction during one specific treatment fraction, we first transform the planning CT using the appropriate registration parameters and then reslice the transformed planning CT to obtain a new “treatment” CT with the same slice thickness and Hounsfield unit information as the planning CT. The position of the cochlea in the treatment CT correctly reflects their position with respect to the treatment machine on the day of treatment. To generate cochlea structures in the treatment CTs, the contours in the original planning CT were used to generate a surface mesh. This was then transformed to the treatment CT and resliced to generate the new contours. Since the planning system regards the cochlea volume as a set of cylindrical prisms based on the contours in each slice, reslicing from the planning CT to the treatment CT introduced a small uncertainty in the cochlea volume due to the finite slice thickness. To evaluate the resulting uncertainty of the cochlea volumes due to reslicing, we calculated the standard deviation of the cochlea volumes on all the treatment CTs and found this to be $\pm 2.8\%$.

Using the MSKCC inhouse treatment planning software (Metropolis), treatment beams were transferred to the rotated and translated CT and used to calculate the delivered dose distribution and DVH for the cochlea on the day of the CBCT scan. DVHs were calculated from 5000 quasirandomly placed points placed inside the contours of each cochlea. The doses at these points were interpolated from a dose distribution calculated on a 2 mm grid. We assume that the distribution of uncertainties in cochlea doses deduced from the registrations without KV radiograph corrections represent those present on days when no images were taken.

Using the registration of each pretreatment CBCT to the planning CT, the total 3D dose distribution after a given number of fractions was accumulated, voxel by voxel, on the planning CT. The cochlea volume uncertainty from the slicing processing will be canceled out when registering volumes back to the planning CT at this step. The dose uncertainty introduced by volume uncertainty is negligible. Similarly, the accumulated DVH, mean dose (D_{mean}), D_{95} , D_{05} , and maximum dose (D_{max}) to the cochlea after a given number of fractions were calculated. For example, the mean accumulated dose $S(n_f)$ can be calculated using

$$S(n_f) = \sum_{i=1}^{n_f} \overline{D}_i / n_f, \quad (2)$$

where $\overline{D}_i$ is the mean dose to the cochlea at fraction i , n_f is the total number of imaging fractions. In this study n_f ranges from 4 to 7 (as shown in Table I).

3. RESULTS

3.A. Setup errors

We calculated the COG of the left and right cochlea and measured the translation and rotation for individual patient and all patients in the study with or without KV radiographic imaging-based correction at patient setup. Then we used the

TABLE II. Mean translational setup errors and their standard deviations combining left and right cochlea for each patient with and without using radiographic imaging. The first number is the mean of setup error. The second number is the standard deviation of setup error. The mean and SD on the last line are the mean and SD value of all CBCTs from ten patients. SD (Mean) is the SD of the mean values for the ten patients.

Patient	Mean $\pm$ SD (cm)					
	RL		AP		SI	
	With imaging	Without imaging	With imaging	Without imaging	With imaging	Without imaging
1	0.28 $\pm$ 0.31	1.15 $\pm$ 0.62	0.19 $\pm$ 0.25	−0.24 $\pm$ 0.67	−0.02 $\pm$ 0.16	−0.38 $\pm$ 0.64
2	−0.22 $\pm$ 0.32	−0.12 $\pm$ 0.37	0.04 $\pm$ 0.19	−0.04 $\pm$ 0.19	−0.05 $\pm$ 0.13	−0.55 $\pm$ 0.35
3	0.09 $\pm$ 0.25	0.22 $\pm$ 0.17	−0.16 $\pm$ 0.42	0.48 $\pm$ 0.82	0.00 $\pm$ 0.08	−0.14 $\pm$ 0.23
4	0.38 $\pm$ 0.23	−0.01 $\pm$ 0.43	0.23 $\pm$ 0.18	0.10 $\pm$ 0.14	0.14 $\pm$ 0.29	0.16 $\pm$ 0.58
5	0.11 $\pm$ 0.20	0.14 $\pm$ 0.18	0.00 $\pm$ 0.29	0.22 $\pm$ 0.36	−0.02 $\pm$ 0.12	−0.20 $\pm$ 0.23
6	0.50 $\pm$ 0.50	0.77 $\pm$ 0.57	0.11 $\pm$ 0.24	0.39 $\pm$ 0.54	−0.09 $\pm$ 0.19	0.09 $\pm$ 0.37
7	−0.42 $\pm$ 0.28	−0.68 $\pm$ 0.58	0.08 $\pm$ 0.29	0.00 $\pm$ 0.74	0.32 $\pm$ 0.39	−0.14 $\pm$ 0.72
8	−0.04 $\pm$ 0.20	−0.15 $\pm$ 0.21	−0.02 $\pm$ 0.11	−0.10 $\pm$ 0.11	−0.01 $\pm$ 0.07	−0.36 $\pm$ 0.16
9	0.08 $\pm$ 0.14	−0.03 $\pm$ 0.16	0.31 $\pm$ 0.33	0.21 $\pm$ 0.23	−0.21 $\pm$ 0.30	−0.47 $\pm$ 0.55
10	−0.36 $\pm$ 0.59	−0.67 $\pm$ 0.58	0.15 $\pm$ 0.30	−0.28 $\pm$ 0.36	−0.04 $\pm$ 0.12	−0.39 $\pm$ 0.17
Mean $\pm$ SD	0.00 $\pm$ 0.30	0.06 $\pm$ 0.43	0.08 $\pm$ 0.28	0.07 $\pm$ 0.48	0.01 $\pm$.021	−0.24 $\pm$ 0.45
SD (Mean)	0.31	0.57	0.14	0.25	0.14	0.23

measured registration matrix to calculate the setup error of the left and the right cochlea. Table II presents the mean and standard deviation of setup error for individual patients, SD and the mean over all patients. For each patient, we give the mean and SD of all translational shifts of the right and left cochlea COGs over all imaging fractions. The values in the columns marked “with imaging” come from the residual setup errors after kV radiographic image correction. The values in the columns marked “without imaging” come from the setup errors present in the initial setup. The mean over all patients under study constitute a measurement of the systematic errors of the patient immobilization and the imaging system. The standard deviation of individual patient’s setup error is a measure of the interfractional shift of the cochlea for the patient. The standard deviation of the all the patient mean values gives a measure of the systematic error likely to be encountered by individual patients.

Table II shows that the mean translational setup errors for the cochlea of all CBCTs of 10 patients in RL, AP, and SI direction without KV imaging-based correction are (0.06 $\pm$ 0.43, 0.07 $\pm$ 0.48, −0.24 $\pm$ 0.45) cm, combining results for left and right cochlea. With the KV radiographic imaging-based correction during patient setup, the setup error in the superior–inferior direction reduces from −0.24 cm to almost zero, and standard deviation of setup error is reduced by 30%, 42%, and 53% in RL, AP, and SI direction, respectively. The smaller mean setup errors in right–left and anterior–posterior directions are comparable, and represent the systematic error of the mask immobilization system.¹⁰

Scatter plots of the components of the setup errors of the left vs right cochlea, together with their linear correlation coefficients, R^2 , are shown in Fig. 2, with (left column), and without (right column), the KV radiographic correction. Without imaging-based correction, the correlation coefficients in the right–left (Δx , top plot), anterior–posterior (Δy , middle plot), and superior–inferior (Δz , bottom plot)

directions, are $R^2 = 0.98$, 0.80, and 0.77, respectively. When KV radiographic imaging-based correction is used during setup, the corresponding coefficients are 0.95, 0.65, and 0.37, respectively. We find the largest translational setup error is along the right–left direction, and the smallest is along the superior–inferior direction. Before imaging-based correction, the setup error has a strong correlation in right–left direction ($R^2 = 0.98$), suggesting that translational error dominates in this direction. There are weaker correlations along superior–inferior direction ($R^2 = 0.77$) and anterior–posterior direction ($R^2 = 0.80$), indicating more contribution from the rotation in this direction. With imaging-based correction, the dominant error in the anterior–posterior and superior–inferior directions is the residual rotational error.

Table III shows the rotational setup error of ten patients. The mean of rotation is (0.06 $\pm$ 3.57, −0.16 $\pm$ 3.64, 0.06 $\pm$ 3.09) degree around the rotation of x, y, and z axes. The mean values of rotation are around zero with variation around 3°. We note that these rotational errors are dependent on the chosen location of the axis of rotation (in our case the center of the CT image set). We also included the mean and standard deviation of Θ , the magnitude of the rotation angle between the line of separation of the cochlea cogs on the planning and treatment CTs. For all patients under study, mean of Θ is 1.83° $\pm$ 1.28°. Figure 3 shows distribution of Θ for each individual patient.

We also calculated the magnitude of the shift of each cochlea COG from its planning position. Figure 4 shows the distribution of these shifts from the 52 CBCTs of the 10 patients (top). Using KV radiographic imaging-based correction at patient setup moves the peak of the distribution of shifts to significantly smaller values ($p < 0.01$). From these histograms, we measured mean shift magnitudes of the cochlea of 0.48 cm with and 0.79 cm without KV radiographic imaging-based correction. Also shown in Fig. 4 (bottom) are the mean value (and standard deviation) of the

FIG. 2. Correlations between set up errors of the left and right cochlea in x(RL, top), y(AP,middle), and z(SI, bottom) directions. Horizontal axis is the translation of left cochlea; vertical axis is the translation of right cochlea. Setup error was calculated with (left) and without (right) KV radiographic imaging-based correction.

magnitudes of each individual patient's shifts with vs without KV radiographic imaging-based correction. In all patients, these are seen to reduce with KV radiographic imaging-based correction ($p < 0.01$).

3.B. Accumulated dose to the cochlea

We calculated the planned dose to cochlea per fraction and the dose delivered to the cochlea per fraction using the

TABLE III. Mean rotational setup errors and their standard deviations for each patient. The first number is the mean of setup error. The second number is the standard deviation of setup error. The mean and SD on the last line is the mean and SD value of all CBCTs from ten patients. SD (Mean) is the SD of the mean values for the ten patients. R_x , R_y , R_z are the rotational angles around x, y, z axes placed at center of CT. Θ is the magnitude of the rotational angle between the line of separation of the cochlea cogs on the planning and treatment CTs.

Patient	Mean $\pm$ SD (degree)			
	R_x	R_y	R_z	Θ
1	-0.06 ± 1.32	1.44 ± 1.16	1.07 ± 0.77	2.02 ± 1.09
2	0.54 ± 0.67	-1.81 ± 1.41	-0.22 ± 0.23	1.50 ± 0.56
3	-0.46 ± 1.60	0.98 ± 0.44	3.43 ± 1.49	3.33 ± 1.11
4	0.54 ± 0.68	-1.81 ± 1.41	-0.22 ± 0.23	2.69 ± 1.88
5	-0.31 ± 0.86	-0.26 ± 0.56	-0.52 ± 0.77	1.39 ± 0.51
6	0.57 ± 1.97	-0.16 ± 0.25	0.10 ± 0.56	0.90 ± 0.98
7	-1.22 ± 0.75	1.73 ± 1.56	-0.42 ± 1.81	NA
8	-0.35 ± 0.18	-0.34 ± 0.82	-0.12 ± 0.87	0.81 ± 0.74
9	0.50 ± 1.59	-1.69 ± 1.03	-1.73 ± 1.22	2.91 ± 1.44
10	-0.01 ± 0.88	0.15 ± 1.24	-0.77 ± 1.00	1.45 ± 0.93
Mean $\pm$ SD	0.06 ± 1.26	-0.16 ± 1.58	0.06 ± 1.60	1.83 ± 1.28
SD (Mean)	1.09	1.06	0.95	0.9

treatment CT, using MSKCC's inhouse "research" treatment planning software Metropolis. Figure 5 shows the dose volume histograms (DVHs) of delivered and planned dose per fraction to cochlea for patient 2 with 7 CBCTs and one planning CT, from the setup with and without imaging-based correction, shown in the top and bottom figures, respectively. The variation in treated dose is noticeably larger without the KV-based correction.

Table IV shows the planned and average delivered mean dose to the cochlea (D_{mean} and S_{mean}) per fraction for the n_f imaging fractions with and without KV imaging-based correction. The overall reduction in size of the difference in

FIG. 3. The magnitude and standard deviation of the rotational angle between the line of separation of the cochlea cogs on the planning and treatment CTs for each individual patient (Patient 7 is not plotted due to missing one cochlea).

FIG. 4. Histograms of the magnitude of the spatial shift (cm) of the left and right cochlea, with (Top left, all patient), without (Top right, all patient) KV radiographic imaging-based correction and each individual patient's mean and standard deviation with vs without KV radiographic imaging-based correction (bottom). Each shift is the displacement of the cochlea COG found from the registration transformation, including rotations. Patient population distributions of shifts (top left and right) are significantly different (T -test, $p < 0.01$). Difference between average shifts for each patient with and without KV radiographic imaging-based correction is significantly different from zero [signed rank test (Ref. 14) $p < 0.01$].

FIG. 5. DVHs of the right cochlea dose per fraction for one patient as calculated on the planning and treatment CTs, based on the patient's planned and seven treatment positions from CBCT scans, together with the accumulated dose per fraction for the seven fractions with CBCT images. The two thick lines show the planned dose (brown) and accumulated dose (blue) to cochlea. (Top) patient setup with KV radiograph. (Bottom) without KV radiograph.

planned and delivered doses seen in Table IV with the use of KV radiographic imaging was statistically significant (T -test, $p < 0.01$). Table V lists the population median and range of the difference between D_{mean} and S_{mean} , D_{95} and S_{95} , and D_{05} and S_{05} with and without imaging-based correction, where S is defined in Eq. (2). Comparing results without and with KV radiographic imaging, we found the median (range) of the magnitude of the difference between the planned and accumulated mean dose per fraction changes from 6.25 (0.8–32.4) cGy to 3.28 (0.39–9.86) cGy for left cochlea ($p = 0.04$), and 14.7 (3.6–27.9) cGy to 5.25 (0.8–16.8) cGy for right cochlea ($p = 0.01$) with KV radiographic imaging. Figure 6 plots the percentage difference of $S_{\text{mean}}(n_i) - D_{\text{mean}}^{\text{planned}}$ as function of number of imaging fractions i . The uncertainty in average delivered dose to cochlea decreases as the number of imaging fractions accumulated increases, and this effect is generally clearer for the kV imaging corrected data. We also see a reduction in mean setup error with the benefit of KV imaging in Table II.

4. DISCUSSION

4.A. Uncertainty from pencil beam dose calculation algorithm

To estimate dose uncertainties that may result from use of the pencil beam algorithm in a small structure like the cochlea that contains bone and air interfaces, we compared our MSKCC inhouse pencil beam algorithm (with a 2 mm dose grid and inhomogeneous correction) with Monte Carlo dose calculation¹¹ (using the same 2 mm dose grid, with 0.7 MeV electron energy and 0.01 MeV photon energy cut-off). Figure 7 shows the comparison of DVHs from the Monte Carlo and Pencil Beam algorithms. The mean doses are: 42.33 cGy (left, Monte Carlo), 42.50 cGy (left, Pencil Beam),

TABLE IV. Planned mean dose and accumulated mean dose per fraction to left and right cochlea for the patient setup with and without imaging-based correction.

Patient	Left cochlea (cGy)			Right cochlea (cGy)		
	Planned dose per fraction D_{mean}	Accumulated dose per fraction S_{mean}		Planned dose per fraction D_{mean}	Accumulated dose per fraction S_{mean}	
		With radiographic imaging	Without radiographic imaging		With radiographic imaging	Without radiographic imaging
1	136.7	133.8	113.6	115.1	110.1	144.6
2	140.5	146.6	174.0	124.6	123.8	133.9
3	89.1	95.0	93.2	75.3	70.0	83.5
4	16.3	15.3	13.7	122.3	130.6	142.4
5	117.3	122.2	136.7	132.0	134.9	153.4
6	110.3	120.2	119.3	185.9	169.1	182.3
7	108.8	106.1	109.1	NA	NA	NA
8	41.8	38.9	66.7	61.6	59.8	92.2
9	137.3	137.6	137.8	143.6	133.1	128.5
10	122.6	118.9	123.4	201.9	196.5	189.4

TABLE V. Median and range of patient distribution of the magnitude of differences between patient accumulated dose delivered and the planned dose for setup without or with imaging-based correction.

	S _{max} -D _{max} median (range)		S _{mean} -D _{mean} median (range)		S ₉₅ -D ₉₅ median (range)		S ₀₅ -D ₀₅ median (range)	
	With imaging	Without imaging	With imaging	Without imaging	With imaging	Without imaging	With imaging	Without imaging
Left (%)	7.06 (0.58–18.9)	16.2 (0.9–29.4)	4.21 (0.28–8.94)	11.7 (0.7–63.6)	3.74 (0.26–12.8)	9.1 (1.6–26.5)	6.29 (0.48–11.7)	15.9 (0.5–50.7)
Left (cGy)	8.66 (1.0–16.0)	14.3 (1.4–40.2)	3.28 (0.39–9.86)	6.25 (0.8–32.4)	2.18 (0.29–11.8)	4.4 (1.0–18.1)	7.55 (0.78–11.8)	11.8 (0.7–47.7)
Right (%)	4.01 (0.61–9.08)	8.2 (0.8–11.1)	4.34 (0.65–9.06)	10.2 (2.0–45.4)	4.90 (0.33–34.8)	18.7 (2.6–60.0)	5.68 (0.35–25.3)	8.4 (0.6–31.4)
Right (cGy)	7.07 (1.3–19.2)	12.3 (1.7–17.1)	5.25 (0.8–16.8)	14.7 (3.6–27.9)	4.54 (0.36–28.5)	13.8 (4.4–42.9)	6.67 (0.51–28.1)	10.4 (0.9–34.9)

61.69 cGy (right, Monte Carlo), and 62.22 cGy (right, Pencil Beam). Results from Pencil Beam with inhomogeneity correction are within 1% of the Monte Carlo simulation.

4.B. Relationship with rotational and translational setup errors

The translational and the rotational setup errors are not independent in the head and neck cancer patients. The largest translational setup error is in left and right direction and the smallest in superior–inferior direction. The largest rotational setup error is the rotation around the RL and AP axes. With assistance of KV radiographic imaging, the standard deviation

of spatial shift can be reduced by about 2 mm in each direction. The residual setup error is largely related to rotations around the SI and AP directions. The correlation of translational and rotational errors is related to the separation of the left and right cochlea and also the location of the center of rotation. In this study, we found the separation of COGs of the left and right cochlea ranges from 65 to 83 mm, with mean value of at 72.9 ± 5.9 mm. A 1.5° rotation around superior–inferior direction will introduce 1 mm translational error in AP direction, as shown in Fig. 8.

We performed a linear fit of the average magnitude of the translational setup error for both cochlea (before and after KV radiographic-imaging based setup) to the separation of left and right cochleas. From the slope of the fit, as the separation increased by 1 cm, we found the setup error increased by 0.12 ± 0.06 and 0.63 ± 0.06 cm with and without KV radiograph correction, respectively (Fig. 8). Figure 2 also shows the relationship between the translational and rotational setup errors.

4.C. Setup error and the uncertainty of dose to the cochlea

Setup error will be reduced in a statistically significant way with the assistance of KV radiographic imaging-based correction Fig. 4 (bottom). We can reduce the setup error of the cochlea by up to 2 mm with imaging-guided setup. For multifractional IMRT treatment, setup with KV radiographic image-based correction would bring clinical

FIG. 6. Absolute magnitude of percentage of $\text{RMS}(S(n_i) - D_{\text{mean}}^{\text{planned}}) / D_{\text{mean}}^{\text{planned}}$ as function of the number of accumulated imaging fractions n_i , for the patient setup without (top) and with (bottom) KV imaging-based correction.

FIG. 7. Monte Carlo vs Pencil Beam algorithm: Both 2 mm dose grid. Monte Carlo electron energy cut 0.7 MeV, photon energy cut 0.01 MeV.

FIG. 8. Correlation between average magnitude of the translational setup error of left and right cochlea and cochlea separation. (Left) The cochlea shift as measured after patient setups are corrected with imaging-based correction. (Right) without imaging-based correction.

benefit over the standard clinical procedure of imaging once weekly.

The correlation between the setup error and the uncertainty of cochlea dose depends on patient, PTV geometry, choice of beam arrangement and other factors. Use of imaging-guided patient setup can reduce the dose uncertainty. The overall reduction in size of the difference in planned and delivered doses seen in Table IV with the use of KV radiographic imaging is statistically significant (T -test, $p < 0.01$). This will further decrease¹² as the number of fractions increases (Fig. 6).

4.D. Hearing loss and uncertainty of dose to cochlea

Recent studies^{2-7,13} report that SNHL (variously defined in terms of bone-conduction thresholds, Δ BCTs, at different frequencies) was observed when the mean cochlea dose was 4000 cGy or larger. At 5000 cGy to the cochlea, studies show the probability of SNHL is 0.38 (Chen,⁴ Δ BCT ≥ 20 dB at ≥ 1 year), 0.33 (Honoré *et al.*,⁶ Δ BCT ≥ 20 dB at ~ 0.5 –6.5 years), 0.18 (Pan *et al.*,³ Δ BCT = 20 dB at 1 year) at 4 kHz, and 0.26 (van der Putten,⁷ Δ BCT > 15 dB at 2–7 years for at least three frequencies between 0.25–12 kHz). At 4000 cGy to the cochlea, the probability of SNHL is 0.38 (Chen⁴), 0.30 (Honoré *et al.*,⁶), 0.1 (Pan *et al.*,³) at 4 kHz, and 0.26 (van der Putten⁷), with all SNHL definitions as before. Oh *et al.*⁵ found that hearing loss (Δ BCT ≥ 15 dB from base line) was associated with the total dose delivered to the inner ear when it was greater than 6300 cGy. van der Putten *et al.*⁷ found that the probability of SNHL (defined as before) increased from 0.68 to 1.0 when the mean cochlea dose increases from 5600 to 6800 cGy. Based on the NTCP model fitted by van der Putten ($D_{50} = 5320$ cGy, $\gamma_{50} = 2.74$, $D_{10} = 4200$ cGy),^{2,7} the increases in probability of SNHL is $\Delta p = 5.2 \times 10^{-4}$ /cGy for the dose of 5000 cGy to the cochlea. All these studies show that uncertainty of cochlea dose might play an important role in hearing loss for the head and neck patients with planned cochlea dose larger than 5000 cGy.

To estimate uncertainties in the final treated dose after all fractions are delivered is beyond the scope of this paper. However, assuming the uncertainties found in Tables IV and V remain at the end of treatment, we estimate a worst case uncertainty in the rate of SNHL. We had 1 left cochlea and 3 right cochlea in this study with mean cochlea dose greater than 5000 cGy, and 4 left cochlea and 6 right cochlea had mean cochlea dose greater than 4000 cGy. Based on the limited number of CBCTs in our study, the largest difference between accumulated cochlea mean dose to the planned mean cochlea dose is $\sim 5\%$ or 15% of the planned dose for setup with and without KV radiographic imaging-based correction, respectively. For planned cochlea doses of 50 Gy, this is ~ 2.5 and 7.5 Gy with and without KV radiographic imaging-based correction, respectively. Based on the van der Putten model, the resulting worst case uncertainty in the incidence of SNHL is 12% (with KV radiographic imaging-based correction) or 36% (without KV radiographic imaging-based correction). We expect these numbers to be an overestimate, considering that they are based on uncertainties in accumulated dose over only ~ 5 fractions.

5. CONCLUSIONS

We present setup error based on 52 CBCT scans and 10 planning CTs from 10 head and neck cancer patients treated with IMRT at MSKCC. To our knowledge, this study of setup error on dose to the cochlea is unique in that it is the first to address this effect. Studies of setup error usually concentrate on locating the tumor or isocenter, in our case, due to the distance of the cochlea from the isocenter, rotational effects and deformation of the neck introduce additional setup error in the position of the cochlea. This data set represents all the clinical data available at our institution that could be used to investigate the effects. Although limited in number, the study has yielded valuable information on the importance of radiographic setup in minimizing cochlea dose uncertainties. As can be seen from Table II and Fig. 4 (bottom), all patients showed the benefit in setup.

A treatment CT was generated using measured setup error and the planning CT to calculate dose to cochlea. The dose distribution on each treatment CT was accumulated to the planning CT. We found significant differences between the planned dose and the average accumulated mean dose ranges if no imaging was used: 6.25 (0.8–32.4) cGy for left cochlea, 14.7 (3.6–27.9) cGy for right cochlea. With the assistance of weekly KV radiographic imaging-based correction during patient setup, the difference between average accumulated mean doses significantly reduces to 3.28 (0.39–9.86) cGy for left cochlea, 5.25 (0.8–16.8) cGy for right cochlea.

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