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Water equivalent path length calculations using scatter-corrected head and neck CBCT images to evaluate patients for adaptive proton therapy

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Abstract

Proton therapy has dosimetric advantages due to the well-defined range of the proton beam over photon radiotherapy. When the proton beams, however, are delivered to the patient in fractionated radiation treatment, the treatment outcome is affected by delivery uncertainties such as anatomic change in the patient and daily patient setup error. This study aims at establishing a method to evaluate the dosimetric impact of the anatomic change and patient setup error during head and neck proton therapy. Range variations due to the delivery uncertainties were assessed by calculating water equivalent path length (WEPL) to the distal edge of tumor volume using planning CT and weekly treatment cone-beam CT (CBCT) images. Specifically, mean difference and root mean squared deviation (RMSD) of the distal WEPLs were calculated as the weekly range variations. To accurately calculate the distal WEPLs, an existing CBCT scatter correction algorithm was used. An automatic rigid registration was used to align the planning CT and treatment CBCT images, simulating a six degree-of-freedom couch correction at treatments. The authors conclude that the dosimetric impact of the anatomic change and patient setup error was reasonably captured in the differences of the distal WEPL variation with a range calculation uncertainty of 2 %. The proposed method to calculate the distal WEPL using the scatter-corrected CBCT images can be an essential tool to decide the necessity of re-planning in adaptive proton therapy.

Introduction

Radiation therapy, using either photon or proton beams, is a clinically accepted technique to treat head and neck cancer patients. Intensity-modulated radiation therapy (IMRT) and intensity-modulated proton therapy (IMPT) are advanced radiotherapy techniques capable of delivering highly conformal dose to tumor volumes while sparing organs-at-risk (OARs). Recently, it has been demonstrated that IMPT has advantages of sparing critical organs compared to IMRT while maintaining reasonable dose conformity to tumor volumes (Stenecker *et al* 2006, van de Water *et al* 2011, Kandula *et al* 2013, Holliday *et al* 2015).

For fractionated radiotherapy of head and neck cancers, anatomic changes (Barker *et al* 2004, Lee *et al* 2008b) and the resulting dosimetric impacts have been reported (Lee *et al* 2008a). Utilizing weekly CT scans, Barker *et al* reported that gross tumor volume (GTV) decreases at a median rate of 1.8 % per day, which corresponds to a median total volume

loss of 69.5 %. In a study by Lee *et al* 2008b, in which anatomic changes were estimated by daily MVCT images, similar results for parotid glands were found: a median volume loss of 0.7 % per day and a median total shift of 5.3 mm towards the center of the patient body. As a dosimetric consequence, Lee *et al* 2008a retrospectively estimated that 3 of 10 patients received 10 % higher dose on parotid glands than planned.

In addition to anatomic changes, large patient setup uncertainties, measured for bony structures, have been reported for the head and neck region (Zhang *et al* 2006, Ahn *et al* 2009, van Kranen *et al* 2009). Specifically for photon radiation therapy, dosimetric impacts of patient setup uncertainties were investigated in previous studies (Hong *et al* 2005, Siebers *et al* 2005).

Similarly to the adverse impact of anatomic changes, patient setup uncertainties can result in underdosing the GTV and overdosing the healthy tissues.

Proton therapy, characterized by a rapid fall-off at the distal edge, can be more sensitive to dose delivery uncertainties than photon radiotherapy. Therefore, investigating the dosimetric impact of the uncertainties during proton therapy has gathered interest (Lomax *et al* 2008a, Lomax *et al* 2008b, Kraan *et al* 2013). The dosimetric effect of anatomical and setup uncertainties were studied in Kraan *et al* 2013 using a replanning CT acquired in the middle of the treatment schedule.

Using daily cone-beam CT (CBCT) imaging can capture the full extent of anatomic changes over the entire course of treatment and the dosimetric variations caused by the inter-fractional setup uncertainties. However, proton dose calculation on the CBCT image has been hindered by the inaccurate Hounsfield units (HU) of the CBCT images, stemming mainly from scatter artifacts (De Marzi *et al* 2013). To resolve this issue, multiple studies (Kurz *et al* 2015, Landry *et al* 2015, Veiga *et al* 2015, Veiga *et al* 2016, Wang *et al* 2016) have calculated doses and water equivalent path length (WEPL) on the virtual CT images, planning CT (pCT) images deformed to the treatment CBCT images by using deformable image registration (DIR). Landry *et al.* demonstrated the feasibility of the method by comparing proton doses calculated on the virtual CT and re-planning CT with a mean WEPL difference below 1 mm with a standard deviation of 2.6 mm. However, the deformed pCT-based dose calculation is sensitive to DIR errors, for instance, caused by air pockets (Niu *et al* 2012).

Previously, a scatter correction algorithm was developed for CBCT image reconstruction utilizing the pCT as *a priori* information (Niu *et al* 2010, Niu *et al* 2012). More recently, this scatter correction method has been validated for proton dose calculations and was demonstrated to be less sensitive to anatomic variations of weight loss and air pockets (Park *et al* 2015 and Kurz *et al* 2016).

The objective of this study is to establish a method of estimating the dosimetric impact of anatomic changes for proton therapy with the presence of patient setup error for head and neck patients. To date, there have been no reports utilizing regular (daily or weekly) CBCT images to directly assess the dosimetric variations of proton therapy on a cohort of head and neck cancer patients due to the anatomic changes and setup uncertainties. This study utilizes

a previously validated CBCT artifact reduction algorithm to generate CBCT data useful for proton dose calculations and analyzes the dosimetric variations in 13 head and neck cancer patients over the entire course of treatment.

Materials and Methods

A. Image Data

Tomographic imaging data of 13 head and neck cancer patients who received photon radiotherapy and CBCT exams on a weekly basis were included in a retrospective study. For each patient, a planning CT (pCT) image and 5–7 weekly CBCT images were available. The pCT images were acquired using a large bore GE CT scanner (140 kVp tube voltage, 0.6–1.1 mm pixel size, 2.5 mm slice thickness). The CBCT images were obtained using an Elekta XVI system (100 kVp tube voltage, 10 mA tube current, 10 ms exposure time, no bowtie filter, small panel position (centered detector, full fan) with 20 cm collimator). Each pair of the pCT and weekly CBCT images were used for the CBCT scatter correction, so that the scatter-corrected CBCT (cCBCT) images were generated with an image size of (400, 400, 200) and a voxel dimension of (1.0, 1.0, 1.0) [mm].

B. Scatter Correction of CBCT Images

Since scatter correction of CBCT images is essential for accurate WEPL calculation on the images, an existing method was utilized (Park *et al* 2015). In this algorithm, scatter in CBCT was estimated from *a priori* information given by the deformed pCT images obtained via DIR. The scatter correction algorithm uses the deformed pCT images to generate a reference projection image and has been demonstrated to be minimally affected by the accuracy of the DIR employed in the algorithm.

In the algorithm, the scatter correction is achieved by using the following equations:

$$I_{sca} = f(CF \times I_{raw} - I_{pri}) \quad (1)$$

$$I_{corr} = CF \times I_{raw} - I_{sca} \quad (2)$$

where I_{sca} is the scatter projection intensity, I_{raw} is the original projection intensity, I_{pri} is the forward projection intensity of the deformed pCT image, and I_{corr} is the corrected projection intensity from which the cCBCT images are reconstructed. The scatter images are obtained by subtracting the primary beam projections, which are forward-projection images of the deformed pCT image from the original CBCT projections. A smoothing filter f that consists of a median filter and a Gaussian filter was applied to the subtraction result. Smoothing the scatter images removes high frequency contributions of DIR errors, making the algorithm robust to such uncertainties. CF represents a calibration factor to match intensity levels between the pCT and CBCT images.

An in-house code developed in Park *et al* 2015 was used. The CF, defined as the ratio of the exposure current-time products ($\text{mAs}_{\text{ref}}/\text{mAs}$), was set to be 19.2 ($= 64 \text{ mA} \times 30 \text{ ms}/(10 \text{ mA} \times 10 \text{ ms})$) for all patient cases. For more details on the scatter correction method, the interested reader may refer to Park *et al* 2015.

B.1 Automatic Rigid Registration—Automatic rigid registrations were performed prior to DIR in order to (1) reduce the computational cost for the DIR, and (2) simulate a possible patient setup for proton therapy. A six degree-of-freedom (DOF) couch correction was simulated by performing an automatic rigid registration and using the resultant translation/rotation. The scatter-corrected CBCT image transformed by the 6 DOF couch correction, called $\text{cCBCT}_{\text{rigid}}$, describes the patient anatomy positioned for treatment. For the automatic rigid registration, mean squared error (MSE) was used to measure the image similarity between the pCT and CBCT images. The image similarity was calculated only inside a cylindrical mask of 130 mm radius centered at the isocenter, excluding the regions outside the CBCT field of view (FOV). Using this cylindrical mask could help to prevent potential registration errors affected by the intensity values around the FOV border. Plastimatch, an open source software package for image computation, was utilized to run the automatic rigid registration (Shackelford *et al* 2010). The accuracy of the automatic rigid registration was verified by visually comparing pCT and $\text{cCBCT}_{\text{rigid}}$.

B.2 Deformable image registration—Following the 6 DOF rigid registration, a deformable image registration implemented in Plastimatch was used to register each $\text{cCBCT}_{\text{rigid}}$ image to the pCT image. The resultant deformed pCT image by the DIR served as *a priori* information for the scatter correction. The transformation was interpolated by using cubic B-spline basis functions with a grid spacing of 30 mm in all directions. The DIR was performed in a single-resolution framework with the images down-sampled by a factor of (2, 2, 1). A cylindrical mask was used as in the automatic rigid registration. MSE was chosen for image similarity metrics for the DIR. In the process of calibrating the scatter correction algorithm, mutual information (MI) was also tested. Each registration was stopped after maximum 30 iterations unless it converged by other criteria.

C. Comparison of DIR Cost Functions

In order to compare the impact of different image similarity metrics, MSE and MI, on the scatter correction of CBCT images, an angular WEPL calculation was performed. At the isocenter of the $\text{cCBCT}_{\text{rigid}}$ images registered to the pCT image, WEPLs were calculated for a range of posterior oblique beam angles ($90\text{--}135^\circ$ and $225\text{--}270^\circ$), which is representative of our clinical beam arrangement for head and neck proton therapy. This angular WEPL calculation was also performed on (1) pCT image, (2) $\text{cCBCT}_{\text{rigid}}$ images generated using the MI-based DIR, and (3) $\text{cCBCT}_{\text{rigid}}$ using the MSE-based DIR. The WEPL calculation on the pCT was used as a reference, to which the WEPLs on the scatter-corrected images were compared.

WEPLs were calculated by using uniform step-based ray tracing (Phillips *et al* 2014) implemented in the Plastimatch software. In the algorithm, WEPL is calculated by summing up the approximated proton stopping power ratio (Zhang *et al* 2009) multiplied by the

physical length of each step along a proton beam path. An assumption of coplanar and parallel proton beam was made in this study.

D. Distal WEPL Calculation

In proton therapy, it is important to ensure that the distal edge of the tumor volume are well matched with the delivered proton beam ranges during the course of treatment. Therefore, WEPL values calculated to the distal edges of target volume (distal WEPL, hereafter) are most sensitive to anatomic and setup uncertainties and are directly related to the dosimetric impact of anatomic changes in patient.

First, in order to enable distal WEPL calculation, the distal edges of a target volume, i.e. planning target volume (PTV), were derived from physician-defined contours on the pCT images. Prior to the distal WEPL calculation, the 6 DOF correction was made to the cCBCT images. The cCBCT image was transformed by using the rigid body transformation obtained from the automatic 6 DOF rigid registration.

Once the images were aligned and the distal edges were extracted from the tumor contours, the WEPL calculation was performed on the pCT and the cCBCT_{rigid} images. The difference between these distal WEPL on the pCT and each cCBCT_{rigid} image was calculated and defined as distal WEPL difference. The distal WEPL difference calculated to all points belonging to the distal edge was plotted in beam's eye view to visualize WEPL variations over the distal area. The calculation points were irregularly but densely spaced; the average spacing ranged from 0.3 to 1.3 mm. Mean difference and root-mean-squared-deviation (RMSD) of the distal WEPL were calculated to estimate overall change over the distal area. Weekly-varying dosimetric impact was analyzed by comparing the distal WEPL differences calculated for all available treatment fractions.

Results

A. Comparison of DIR cost functions

In Figure 1, some of the skin voxels in the pCT image were aligned to the voxels of the immobilization mask still remained in the cCBCT_{rigid} image by the MI-based DIR. This misalignment with the MI-based DIR resulted in high intensity values (see Figure 2(b)) in the region of the immobilization mask in the cCBCT_{rigid} images as shown in Figure 2. Figure 2(b) and (c) show the comparison of the cCBCT_{rigid} images generated by using the MI-based DIR and the MSE-based DIR, respectively.

The angular WEPLs calculated with the MI-based DIR and MSE-based DIR are compared in Figure 3(b). The WEPL calculation on the cCBCT_{rigid} image with the MSE-based DIR reasonably reflected the volumetric change (Figure 3(a)), in which the impact of weight loss was substantial. On the other hand, the high intensity values obtained with the MI-based DIR compromised the WEPL difference, resulting in underestimation of the WEPL impact of the volume change, e.g. at the angles between 90 and 110 °.

B. Distal WEPL calculation

Figure 4(a) and (b) show a physician-defined target contour and points describing the distal edge (shown as squares and triangles) overlaid on the corresponding axial planes of a pCT image and a cCBCT_{rigid} image (last available weekly fraction) of Patient 1. Comparing the images shows large amount of anatomic variation. It is noted that some parts of the target contour defined on the pCT was located outside the patient at the treatment fraction.

The WEPLs calculated to the distal edge with the pCT image and the cCBCT_{rigid} image were compared in Figure 4(c). Substantial volume shrinkage shown at the last weekly scan was reasonably captured in the decrease in WEPL. The mean difference of the distal WEPL on this axial slice was 10.7 mm, ranging from 4.8 to 36.3 mm. Such large differences occurred when the patient exterior was angled almost parallel to the proton beam direction.

Figures 5 and 6 show variations of the mean difference and RMSD of distal WEPL calculated for all imaging data of 13 patients, respectively. Gradual increase was found both for the mean difference and RMSD values in 9 patient cases out of 13. It is noted that Patient 12 was considered to have no trend since no substantial change in WEPL and no visible change in volume was observed. The influence of patient setup error on the WEPL calculation results can be seen from Figures 5 and 6. For instance, one outstanding outlier is the large value calculated for 2nd Fraction in Patient 9. This relatively large difference at the beginning of treatment resulted from large patient setup error. At the time of setup, the patient was pressed onto one side of immobilization mask, which is opposite to the WEPL calculation region. This large patient setup error was not fully corrected by the 6-DOF correction using the bony anatomy-oriented automatic rigid registration. In addition, variations shown in CBCT scans on consecutive days (3rd–4th fractions in Patient 1, 1st–2nd fractions in Patient 5, 5th–7th fractions in Patient 6, 2nd–3rd fractions in Patient 7, 2nd–4th fractions in Patient 9, 3rd–4th fractions in Patient 11, and 6th–7th fractions in Patient 13), might be attributed to patient setup uncertainty, because anatomical change should be small over a short amount of time. The day-to-day variations of the mean difference and RMSD of distal WEPL calculated from the consecutive CBCT scans were 0.2 ± 3.3 mm and 0.0 ± 3.2 mm.

Table 1 summarizes statistics of the mean difference and RMSD of distal WEPL. An overall increase in the mean distal WEPL difference (mean $\pm$ standard deviation, 3.6 ± 2.4 mm) indicates volumetric reduction in the patients. The maximum of the mean distal WEPL difference was 6.6 ± 3.3 mm (range, 0.8 to 10.5 mm). RMSD was calculated to capture both increase and decrease in the distal WEPL. In other words, the RMSD values then can be interpreted as either overdosing the regions beyond the distal edge or underdosing the tumor volume. The RMSD of distal WEPL was apparently larger than the mean distal WEPL difference (mean $\pm$ standard deviation, 5.6 ± 1.9 mm). The maximum RMSD was 8.4 ± 3.0 mm (range, 3.2 to 12.0 mm).

A representative example of the distal WEPL difference was plotted in beam's eye view (BEV) in Figure 7. The BEV distal WEPL difference maps generated for each weekly treatment fraction were shown for Patient 2. For Patient 2, it can be seen from Figure 7(a) a monotonous increase in the distal WEPL difference; the mean distal WEPL difference also

gradually increased as shown in Figure 5. This trend may be mainly attributed to the anatomic change in patients for all weekly fractions shown in Figure 7(a). Figure 7(b) shows successful 6 DOF setup corrections for this patient.

Discussion

Variations in the distal WEPL difference over weekly treatment fractions can be attributed to two main delivery uncertainties: anatomic change and patient setup error. In some of the patients, e.g. Patient 2, anatomic change may be seen as a dominant factor because setup error is small. On the other hand, no clear trend was seen for some patients. An investigation can be conducted to quantify patient setup error in a separate manner, thereby helping to better understand the dosimetric impact of anatomic change.

The tumor contours defined by physicians on the pCT were used as the target definition on the treatment CBCT images and deformation of the tumor volume was not considered. In other words, the distal edges of the target volume were assumed to be unchanged throughout all treatment fractions despite anatomic changes in patients. Therefore, the distal WEPL differences calculated in this investigation should be interpreted as the dosimetric impact of all anatomic changes except the local deformation of the distal edges, and patient setup uncertainty. It should be noted that the distal WEPL differences calculated using undeformed tumor contours can overestimate dosimetric impact in case that some part of the distal edge is located off the patient geometry at treatments (see Figure 4). Re-defining the target volume on each treatment fractions may improve the accuracy of the dosimetric impact assessed by the distal WEPL difference. However, there is no strong agreement on how the target volume should be defined during radiation treatment. Although automatic contouring using DIR (Lu *et al* 2006, Zhang *et al* 2007) may provide tumor contours corresponding to each treatment fraction, there is a possibility that it introduces another uncertainty on the target volume definition.

Although proton dose calculation using CBCT is promising, a limitation is the relatively small field size of CBCT images. For instance, the inferior-superior range of CBCT is limited compared to pCT. In case of treating a tumor volume spread over a wide geometric range in the inferior-superior direction, it is not feasible to estimate dose changes all over the tumor area. However, the dosimetric impact can be estimated within the CBCT axial range covering most of cervical vertebral regions. This estimation is still useful to assess the quality of proton therapy.

Another limitation of this investigation is that only one beam direction, a posterior oblique angle on the tumor site, was considered for the WEPL calculations. Fully understanding the effect of anatomic change and patient setup error on the proton dose delivered to the patient will require additional research. In a future study, more practical beam arrangements with a set of several angles may be considered. Moreover, finding proton beam directions which are robust to anatomic change and patient setup error will be an interesting research topic.

It should be noted that the calculated WEPL differences estimate the possible underdosing of the tumor volume and overdosing healthy surrounding tissues in the distal region of the

target. A further study will need to be carried out to find correlations between WEPL-based measures and dosimetric changes to define appropriate thresholds for adaptive replanning as reported in recent studies (Yu *et al* 2016, Matney *et al* 2016, Veiga *et al* 2016, Wang *et al* 2016).

Dosimetric impact was analyzed for two dose delivery uncertainties during fractionated head and neck proton therapy. In addition to anatomic change and patient setup error considered in this study, proton dose delivery quality can be negatively affected by dose calculation errors (Lomax *et al* 2008a): error in dose calculation algorithm and conversion error between CT number and stopping power ratio. This indicates a possibility that dose delivery quality may be further degraded by dose calculation errors. Uncertainty has been taken into consideration by introducing a proper range margin, e.g. 3.5 % + 1 mm at the Massachusetts General Hospital (Paganetti *et al* 2012). In case that dose delivery error is larger than the margin introduced, re-planning may be needed to adequately treat head and neck cancer patients using proton beams as proposed by Veiga *et al* 2016.

Conclusion

Scatter-corrected CBCT images can be used to compute WEPL to the target distal edge, and thereby estimate weekly proton range variations due to anatomic change and patient setup error. The dosimetric impact evaluated by calculating the differences in the distal WEPL can be used to assess the treatment quality of the proton therapy and to determine whether re-planning is necessary for adaptive proton therapy.

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References

- Ahn PH, Ahn AI, Lee CJ, Shen J, Miller E, Lukaj A, Milan E, Yarpalvi R, Kalnicki S, Garg MK. Random positional variation among the skull, mandible, and cervical spine with treatment progression during head-and-neck radiotherapy. *Int J Radiat Oncol Biol Phys.* 2009; 73:626–33. [PubMed: 19147027]
- Barker JL, Garden AS, Ang KK, O'Daniel JC, Wang H, Court LE, Morrison WH, Rosenthal DI, Chao KC, Tucker SL, Mohan R. Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system. *Int J Radiat Oncol Biol Phys.* 2004; 59:960–70. [PubMed: 15234029]
- De Marzi L, Lesven C, Ferrand R, Sage J, Boule T, Mazal. A Calibration of CT Hounsfield units for proton therapy treatment planning: use of kilovoltage and megavoltage images and comparison of parameterized methods. *Phys Med Biol.* 2013; 58:4255–76. [PubMed: 23719506]
- Holliday EB, Garden AS, Rosenthal DI, Fuller CD, Morrison WH, Gunn GB, Phan J, Beadle BM, Zhu XR, Zhang X, Hanna E. Proton therapy reduces treatment-related toxicities for patients with nasopharyngeal cancer: a case-match control study of intensity-modulated proton therapy and intensity-modulated photon therapy. *Int J Part Ther.* 2015; 2:19–28.
- Hong TS, Tomé WA, Chappell RJ, Chinnaiyan P, Mehta MP, Harari PM. The impact of daily setup variations on head-and-neck intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys.* 2005; 61:779–88. [PubMed: 15708257]
- Kandula S, Zhu X, Garden AS, Gillin M, Rosenthal DI, Ang KK, Mohan R, Amin MV, Garcia JA, Wu R, Sahoo N. Spot-scanning beam proton therapy vs intensity-modulated radiation therapy for

- ipsilateral head and neck malignancies: a treatment planning comparison. *Med Dosim.* 2013; 38:390–4. [PubMed: 23916884]
- Kraan AC, van de Water S, Teguh DN, Al-Mamgani A, Madden T, Kooy HM, Heijmen BJ, Hoogeman MS. Dose uncertainties in IMPT for oropharyngeal cancer in the presence of anatomical, range, and setup errors. *Int J Radiat Oncol Biol Phys.* 2013; 87:888–96. [PubMed: 24351409]
- Kurz C, Dedes G, Resch A, Reiner M, Ganswindt U, Nijhuis R, Thieke C, Belka C, Parodi K, Landry G. Comparing cone-beam CT intensity correction methods for dose recalculation in adaptive intensity-modulated photon and proton therapy for head and neck cancer. *Acta Oncol.* 2015; 54:1651–7. [PubMed: 26198654]
- Kurz C, Kamp F, Park YK, Zöllner C, Rit S, Hansen D, Podesta M, Sharp GC, Li M, Reiner M, Hofmaier J, Nepl S, Thieke C, Nijhuis R, Ganswindt U, Belka C, Winey BA, Parodi K, Landry G. Investigating deformable image registration and scatter correction for CBCT-based dose calculation in adaptive IMPT. *Med Phys.* 2016; 43:5635–46. [PubMed: 27782706]
- Landry G, Nijhuis R, Dedes G, Handrack J, Thieke C, Janssens G, de Xivry JO, Reiner M, Kamp F, Wilkens JJ, Paganelli C. Investigating CT to CBCT image registration for head and neck proton therapy as a tool for daily dose recalculation. *Med Phys.* 2015; 42:1354–66. [PubMed: 25735290]
- Lee C, Langen KM, Lu W, Haimerl J, Schnarr E, Ruchala KJ, Olivera GH, Meeks SL, Kupelian PA, Shellenberger TD, Mañon RR. Assessment of parotid gland dose changes during head and neck cancer radiotherapy using daily megavoltage computed tomography and deformable image registration. *Int J Radiat Oncol Biol Phys.* 2008a; 71:1563–71. [PubMed: 18538505]
- Lee C, Langen KM, Lu W, Haimerl J, Schnarr E, Ruchala KJ, Olivera GH, Meeks SL, Kupelian PA, Shellenberger TD, Mañon RR. Evaluation of geometric changes of parotid glands during head and neck cancer radiotherapy using daily MVCT and automatic deformable registration. *Radiother Oncol.* 2008b; 89:81–8. [PubMed: 18707786]
- Lomax AJ. Intensity modulated proton therapy and its sensitivity to treatment uncertainties 1: the potential effects of calculational uncertainties. *Phys Med Biol.* 2008a; 53:1027–42. [PubMed: 18263956]
- Lomax AJ. Intensity modulated proton therapy and its sensitivity to treatment uncertainties 2: the potential effects of inter-fraction and inter-field motions. *Phys Med Biol.* 2008b; 53:1043–56. [PubMed: 18263957]
- Lu W, Olivera GH, Chen Q, Chen M, Ruchala KJ. Automatic re-contouring in 4D radiotherapy. *Phys Med Biol.* 2006; 51:1077–99. [PubMed: 16481679]
- Niu T, Sun M, Star-Lack J, Gao H, Fan Q, Zhu L. Shading correction for on-board cone-beam CT in radiation therapy using planning MDCT images. *Med Phys.* 2010; 37:5395–406. [PubMed: 21089775]
- Niu T, Al-Basheer A, Zhu L. Quantitative cone-beam CT imaging in radiation therapy using planning CT as a prior: first patient studies. *Med Phys.* 2012; 39:1991–2000. [PubMed: 22482620]
- Paganetti H. Range uncertainties in proton therapy and the role of Monte Carlo simulations. *Phys Med Biol.* 2012; 57:R99–R117. [PubMed: 22571913]
- Park YK, Sharp GC, Phillips J, Winey BA. Proton dose calculation on scatter-corrected CBCT image: Feasibility study for adaptive proton therapy. *Med Phys.* 2015; 42:4449–59. [PubMed: 26233175]
- Phillips J, Gueorguiev G, Shackelford JA, Grassberger C, Dowdell S, Paganetti H, Sharp GC. Computing proton dose to irregularly moving targets. *Phys Med Biol.* 2014; 59:4261–73. [PubMed: 25029239]
- Shackelford JA, Kandasamy N, Sharp GC. On developing B-spline registration algorithms for multi-core processors. *Phys Med Biol.* 2010; 55:6329–51. [PubMed: 20938071]
- Siebers JV, Keall PJ, Wu Q, Williamson JF, Schmidt-Ullrich RK. Effect of patient setup errors on simultaneously integrated boost head and neck IMRT treatment plans. *Int J Radiat Oncol Biol Phys.* 2005; 63:422–33. [PubMed: 16168835]
- Steneker M, Lomax A, Schneider U. Intensity modulated photon and proton therapy for the treatment of head and neck tumors. *Radiother Oncol.* 2006; 80:263–7. [PubMed: 16916557]
- van de Water TA, Lomax AJ, Bijl HP, de Jong ME, Schilstra C, Hug EB, Langendijk JA. Potential benefits of scanned intensity-modulated proton therapy versus advanced photon therapy with

- regard to sparing of the salivary glands in oropharyngeal cancer. *Int J Radiat Oncol Biol Phys.* 2011; 79:1216–24. [PubMed: 20732761]
- van Kranen S, van Beek S, Rasch C, van Herk M, Sonke JJ. Setup uncertainties of anatomical sub-regions in head-and-neck cancer patients after offline CBCT guidance. *Int J Radiat Oncol Biol Phys.* 2009; 73:1566–73. [PubMed: 19306753]
- Veiga C, Alshaikhi J, Amos R, Lourenço AM, Modat M, Ourselin S, Royle G, McClelland JR. Cone-beam computed tomography and deformable registration-based “dose of the day” calculations for adaptive proton therapy. *Int J Part Ther.* 2015; 2:404–14.
- Veiga C, Janssens G, Teng C-L, Baudier T, Hotoiu L, McClelland JR, Royle G, Lin L, Yin L, Metz J, Solberg TD, Tochner Z, Simone CB II, McDonough J, Teo B-KK. First clinical investigation of CBCT and deformable registration for adaptive proton therapy of lung cancer. *Int J Radiat Oncol Biol Phys.* 2016; 95:549–59. [PubMed: 27084664]
- Wang P, Yin L, Zhang Y, Kirk M, Song G, Ahn PH, Lin A, Gee J, Dolney D, Solberg TD, Maughan R, McDonough J, Teo B-KK. Quantitative assessment of anatomical change using a virtual proton depth radiograph for adaptive head and neck proton therapy. *J Appl Clin Med Phys.* 2016; 17:427–40. [PubMed: 28297401]
- Zhang L, Garden AS, Lo J, Ang KK, Ahamad A, Morrison WH, Rosenthal DI, Chambers MS, Zhu XR, Mohan R, Dong L. Multiple regions-of-interest analysis of setup uncertainties for head-and-neck cancer radiotherapy. *Int J Radiat Oncol Biol Phys.* 2006; 64:1559–69. [PubMed: 16580505]
- Zhang R, Newhauser WD. Calculation of water equivalent thickness of materials of arbitrary density, elemental composition and thickness in proton beam irradiation. *Phys Med Biol.* 2009; 54:1383–95. [PubMed: 19218739]
- Zhang T, Chi Y, Meldolesi E, Yan D. Automatic delineation of on-line head-and-neck computed tomography images: toward on-line adaptive radiotherapy. *Int J Radiat Oncol Biol Phys.* 2007; 68:522–30. [PubMed: 17418960]

Figure 1. Checkerboard comparison of raw CBCT (last weekly fraction for Patient 8) and (a) pCT, (b) deformed pCT using the MI-based DIR, and (c) deformed pCT using the MSE-based DIR.

Figure 2.

Above is a comparison of image intensity values at the region of the immobilization mask between (a) pCT, (b), (c) scatter-corrected CBCT images using the MI-based DIR and MSE-based DIR, respectively (Patient 8). Six-DOF couch correction was applied to the scatter-corrected CBCT images.

Figure 3.

(a) Image representing difference between original CBCT (6-DOF corrected) and pCT, (b) comparison of the angular WEPL calculated on the scatter-corrected CBCT images generated using the MI-based DIR and MSE-based DIR, shown in Figure 2(b) and (c).

(a)

(b)

(c)

Figure 4.

Overlaid representation of physician-drawn tumor contour, distal edge (shown as squares and triangles), and axial plane of (a) pCT and (b) last weekly cCBCT_{rigid} of Patient 1. Both the axial images are plotted to represent same spatial extent in order to show volumetric changes. WEPLs calculated to the distal edge are compared in (c).

(a)

(b)

Figure 5.

Variations of mean distal WEPL differences plotted against the time, counted as the days after the planning CT scan. The cohort of the patients is divided to two groups with (a) increasing trend and (b) no trend.

(a)

(b)

Figure 6.

Variations of RMSD of distal WEPL difference plotted against the time, counted as the days after the planning CT scan. The cohort of the patients is divided to two groups with (a) increasing trend and (b) no trend.

Figure 7. Representation of (a) beam's eye view distal WEPL difference map varying across weekly treatment fractions (Patient 2) and (b) difference image ($cCBCT_{rigid} - pCT$) visualizing the patient setup accuracy after the 6 DOF couch correction.

Table 1

Summary of statistics of the mean difference and RMSD of distal WEPL calculated over distal area across the weekly treatment fractions.

	Mean difference		RMSD	
	Mean (mm)	Maximum (mm)	Mean (mm)	Maximum (mm)
Patient 1	6.9	9.6	9.1	12.0
Patient 2	2.9	7.2	5.1	9.4
Patient 3	2.0	5.2	3.7	5.9
Patient 4	0.0	1.1	6.5	7.9
Patient 5	2.8	4.2	3.9	5.0
Patient 6	3.0	4.2	3.8	4.8
Patient 7	3.2	8.2	5.9	10.7
Patient 8	6.0	9.0	6.9	9.8
Patient 9	6.3	10.5	7.1	11.7
Patient 10	2.6	5.5	4.7	7.4
Patient 11	6.0	9.6	7.0	10.9
Patient 12	-0.7	0.8	2.4	3.2
Patient 13	5.8	10.2	6.8	11.3
Mean $\pm$ SD	3.6 $\pm$ 2.4	6.6 $\pm$ 3.3	5.6 $\pm$ 1.9	8.4 $\pm$ 3.0