A novel dose-based positioning method for CT image-guided proton therapy

Joey P. Cheung and Peter C. Park

Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 94, Houston, Texas 77030 and The University of Texas Graduate School of Biomedical Sciences at Houston, 6767 Bertner Avenue, S3.8344, Houston, Texas 77030

Laurence E. Court, X. Ronald Zhu, and Rajat J. Kudchadker

Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 94, Houston, Texas 77030

Steven J. Frank

Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1202, Houston, Texas 77030

Lei Dong^{a)}

Scripps Proton Therapy Center, 9730 Summers Ridge Road, San Diego, California 92121

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Purpose: Proton dose distributions can potentially be altered by anatomical changes in the beam path despite perfect target alignment using traditional image guidance methods. In this simulation study, the authors explored the use of dosimetric factors instead of only anatomy to set up patients for proton therapy using in-room volumetric computed tomographic (CT) images.

Methods: To simulate patient anatomy in a free-breathing treatment condition, weekly time-averaged four-dimensional CT data near the end of treatment for 15 lung cancer patients were used in this study for a dose-based isocenter shift method to correct dosimetric deviations without replanning. The isocenter shift was obtained using the traditional anatomy-based image guidance method as the starting position. Subsequent isocenter shifts were established based on dosimetric criteria using a fast dose approximation method. For each isocenter shift, doses were calculated every 2 mm up to ± 8 mm in each direction. The optimal dose alignment was obtained by imposing a target coverage constraint that at least 99% of the target would receive at least 95% of the prescribed dose and by minimizing the mean dose to the ipsilateral lung.

Results: The authors found that 7 of 15 plans did not meet the target coverage constraint when using only the anatomy-based alignment. After the authors applied dose-based alignment, all met the target coverage constraint. For all but one case in which the target dose was met using both anatomy-based and dose-based alignment, the latter method was able to improve normal tissue sparing.

Conclusions: The authors demonstrated that a dose-based adjustment to the isocenter can improve target coverage and/or reduce dose to nearby normal tissue. © 2013 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4801910>]

Key words: proton therapy, image-guided radiation therapy, setup error, adaptive radiotherapy

I. INTRODUCTION

Proton therapy has the potential for creating conformal dose distributions and delivering lower doses to normal tissues than traditional photon therapy due to its ability to modulate range.^{1,2} However, this advantage also complicates treatment delivery because changes in patient anatomy affect the proton beam's range within the body.^{3,4} This sensitivity to range uncertainties can cause deviations from the planned dose distribution when significant changes in patient anatomy occur during multifractionated radiation therapy.

While image-guidance has allowed for us to position the patient accurately using anatomic landmarks, the resultant dose distribution in the patient is not always apparent and methodologies to obtain this are still being developed.^{5,6} While the static dose cloud approximation is valid for photon

beams in most cases, the same is not true for proton beams:^{7,8} as tissue density and thickness change along the proton beam path, so can the resultant dose distribution (potentially to a substantial degree). In theory, a perfect geometry-based target alignment may not guarantee a good dosimetric coverage for the target in proton therapy because variations of tissue density outside the target may impact the proton dose distribution (depending on the geometry and heterogeneity of the irradiated volume). Current methodologies to mitigate dose variations caused by interfractional patient setup errors include compensator expansion (smearing)⁹ and the inclusion of margins.¹⁰ However, these methods are limited to mitigating only rigid shifts of patient and do not address anatomical changes that can result in tissue shrinkage, deformations, misalignment of anatomical structures outside the target, patient weight loss, etc. Therefore, anatomy-based shift will not be

ideal to correct all of these daily variations. Adaptive planning may be required to compensate for these changes,^{11,12} but adaptive planning requires more resources, such as segmentation of structures, replanning, quality assurance testing, etc., that may not be practical to apply in every fraction. Different patient setup positions will result in different perturbations to the dose delivered.^{13,14} The magnitude of dose perturbations due to anatomical changes is difficult to assess by looking at anatomy alone, and therefore a timely assessment of the dose distribution for the patient under a given setup condition is desirable. These complexities imply that a dosimetric index to assess target and normal tissue dose under the specific delivery geometry may be necessary for proper treatment-day alignment. In other words, image-guidance in proton therapy may differ from traditional photon therapy in that anatomical alignment based on visual imaging information may not always be adequate, and adjustments may need to be made based on dosimetric assessment due to proton range variations caused by anatomic changes.

We hypothesized that dosimetric based objectives are needed to fully optimize the patient setup position in proton therapy. Instead of replanning, our corrective action uses a simple isocenter shift to correct patient setup, similar to image-guided radiation therapy setup but using calculated dose information instead of anatomic information. This will make it more practical to apply in routine treatment. Furthermore, by optimizing patient setup using a dose-based alignment method, we can determine whether adaptive planning is necessary to achieve the clinical goal when a simple realignment of the isocenter is inadequate. To our knowledge, no study has reported the implementation of a dose-based isocenter alignment method for proton therapy or compared it with the conventional, anatomy-based alignment method.

II. METHODS AND MATERIALS

II.A. Patient data set

We selected 15 lung cancer patients treated at our institution between October 2009 and February 2011 that had clinically approved proton plans with only two or three coplanar beams for each treatment fraction. These data were chosen in order to simulate the differences between anatomy-based and dose-based alignment. Lung patients were chosen because the proton dose distribution is more sensitive to anatomy change due to large changes in tumor-to-lung boundaries, making them suitable for the purpose of this study. Each passively scattered proton beam was designed to cover the entire planning target volume. Table I shows the patients' tumor characteristics. Several of the patients were replanned over the course of treatment to mitigate anatomical changes seen in imaging. While some of the patients received adaptive replans during the course of treatment due to large anatomical changes (as indicated in Table I), we only used the original treatment plan for our study to observe the impact of these changes to the treatment and assess the ability of our new method to correct for these changes. The patients selected for this study were a subset of protocol patients who were enrolled in a randomized clinical trial to compare proton therapy and photon IMRT for lung cancer.¹⁵ The treatment plans were created with the following parameters: PTV $D_{99\%} \geq 95\%$ of the prescribed dose; total lung $V_{20\text{ Gy}} \leq 37\%$; total mean lung dose (MLD) $\leq 22\text{ Gy}$; maximum spinal cord dose $\leq 45\text{ Gy}$; and minimizing dose to the esophagus $V_{65\text{ Gy}}$ and $V_{45\text{ Gy}}$ and heart $V_{60\text{ Gy}}$ and $V_{30\text{ Gy}}$. The gross tumor volume (GTV) at individual phases from the four-dimensional CT imaging (4DCT) was used to create the internal gross tumor volume (iGTV),¹⁶ which was expanded by 8 mm and manually edited by the treating physician to become internal target volume

TABLE I. Tumor characteristics.

Patient number	Diagnosis	Tumor location	Beam angles (deg)	Baseline ITV size (cm ³)	Last ITV size (cm ³)	ITV volume change (%)	Fraction of last CT	Replanned?
1	NSC NOS	RUL	0/210/295	331.9	262.6	- 20.9	35	No
2	Adeno	RUL	205/290	1221.9	999.8	- 18.2	35	Yes
3	Squamous	RUL	0/180/245	520.8	426.1	- 18.2	34	No
4	Squamous	LUL	120/200/350	865.4	745.1	- 13.9	18	Yes
5	Squamous	LUL	35/110/350	131.9	122.9	- 6.8	29	No
6	Squamous	RUL	220/250/320	738.6	689.2	- 6.7	33	Yes
7	Adeno	RUL	213/240/325	275.5	282.1	+2.4	31	No
8	Squamous	LLL	35/105/170	323.6	313.5	- 3.1	35	No
9	Squamous	RUL	160/265/320	470.6	398.7	- 15.3	37	Yes
10	Squamous	LUL	35/90/174	531.8	540.6	+1.6	31	No
11	Squamous	RLL	10/255/325	625.3	437.2	- 30.1	29	Yes
12	Adeno	RUL	210/290	149.0	133.1	- 10.7	34	Yes
13	Squamous	LUL	45/160	1405.2	1304.7	- 7.2	29	Yes
14	Squamous	RUL	0/190/345	986.1	843.7	- 14.4	37	Yes
15	Adeno	RUL	170/240/330	314.3	308.4	- 1.9	32	No

Note: adeno = adenocarcinoma; ITV = internal target volume; LLL = left lower lobe; LUL = left upper lobe; NSC NOS = non-small cell carcinoma, not otherwise specified; RLL = right lower lobe; RUL = right upper lobe; squamous = squamous cell carcinoma. "Replanned" refers to the patient receiving at least one full replan during the course of treatment.

FIG. 1. Planned dose distribution and beam angles for patient 1.

(ITV). The PTV was created with a 5 mm uniform expansion of the ITV. A proximal and distal margin of 3.5% of the total water equivalent path length plus 3 mm was added to the ITV along the central beam path to account for range uncertainties, and a lateral expansion of 1.0–1.5 cm to the aperture for the ITV in each beam angle was introduced to account for uncertainty in setup position. An expansion of the compensator was included to compensate for misregistration of heterogeneities.⁹ More details of the treatment planning parameters can be found.¹⁷ Figure 1 shows the planned dose distribution on the treatment planning CT scan for patient 1 of this study. Patients were set up with kV orthogonal planar imaging and immobilized using a wing board with vacuum bag and head holder, and knee and foot cradles.¹⁸

Each of these protocol patients had weekly 4DCT for evaluation during the course of treatment. These repeat CT scans were used to simulate treatment-time images for patient alignment. All of these patients were treated in free-breathing condition. We used the time-averaged 4DCT, which was generated by averaging the CT numbers for ten respiratory phases at each voxel location. To simplify further, we examined the CT image from only the patients' last available weekly CT scans since those scans were expected to have the largest anatomical changes compared with the original treatment planning CT scans. Some of the treatment beams may pass through the CT couch, therefore the CT data representing the imaging couch were replaced with a digital treatment couch using in-house software to properly account for beams that intersected the treatment couch.¹⁹ Contours

from the original planning CT image were propagated to the treatment-time image using in-house deformable image registration software^{20–22} to delineate the patient anatomy at the time of treatment for dose–volume histogram (DVH) calculations. The algorithm was assessed for use in automatic contour propagation for repeat CT and 4DCT imaging and found that interfraction accuracy of 0.4 mm mean absolute surface-to-surface distance and intrafraction accuracy of >98% volume overlap was achievable when compared to the physician-modified contours.²¹

II.B. Anatomy-based alignment

All weekly images were registered to the planning CT image using bony structures in the vertebrae nearest the target to simulate the image guidance technique used at most proton centers today: kilovoltage orthogonal projection imaging, which can detect bony anatomy sufficiently for alignment purposes. This baseline alignment based on bony anatomy was used as the reference to compare with the proposed dose-based alignment and will be referred to as anatomy-based alignment through the rest of this paper. We also obtained alignment positions for the iGTV to check whether our dose-based alignment ended up clustering close to iGTV alignment. These alignments were performed using in-house image registration software with a region-of-interest based alignment method, which is able to achieve submillimeter registration accuracy with disagreements to human adjustments of greater than 3 mm less than 2% of the time.^{22,23}

II.C. Dose-based alignment

For the dose-based alignment, dose metrics need to be extracted from the new treatment day CT image. In order to do this, we need to calculate the dose distributions for a number of couch setup positions with relative patient shifts in the x , y , and z directions from the baseline anatomical alignment. This will allow for the assessment of the impact of the dose delivered for various setup positions in order to find the optimal setup for the patient to achieve the desired target coverage while minimizing dose to normal tissues. Once an optimal shift is established, these coordinate shifts can be applied to the treatment couch to position the patient in the final optimal treatment position.

A full calculation of dose distributions for every possible setup position would require a significant amount of time and/or computational resources that would not be practical for online clinical use. To remedy this problem, we used a recently developed and validated fast dose approximation method⁷ to calculate the dose to organs for different patient positions. This calculation method has been shown to sufficiently account for changes in tissue density accompanying various setup and anatomical changes for the purposes of optimization or quick dose assessment.⁷ Briefly, this dose approximation method is based on water equivalent pathlength (WEPL) range mapping by acquiring relative stopping powers from the nominal and treatment day CT images and remapping the corresponding dose from each proton beamlet from

the original nominal CT to the new moving CT based on the WEPL. Using this method, we recalculated the dose from each beam for multiple isocenter shifts of up to 8 mm in each direction (x , y , and z) in 2 mm increments (based on the dose calculation grid size), resulting in 729 dose calculations per beam angle. The 8 mm search limit was selected because our lateral circular margins for aperture expansion in lung proton therapy are typically 1 cm. This allows us to have some room to shift the patient around with the target still confined within the aperture in the high dose region. This search space may need to be defined differently for different applications to suit the treatment plan design.

To further minimize the computation time required, we calculated doses only for the voxels within the volumes of interest, which included the target volume and the ipsilateral lung in this study. DVHs were obtained from each shift, and were used to determine the optimal alignment. We used the target coverage constraint that 99% of the ITV would receive at least 95% of the prescribed dose ($D_{99\%} \geq 95\%$), and optimized the normal tissue dose by minimizing the mean dose to the ipsilateral lung. If the target coverage constraint was not met, the shift that maximized target coverage was defined as the optimal alignment. The optimality of the target coverage and organ-at-risk doses can be visualized in a solution space plot with nondominated solutions mapped out on a Pareto frontier, which is the set of solutions in which no one parameter can be made better without making the other parameter worse (e.g., lung dose cannot be decreased without reducing target coverage).

Figure 2 shows the general workflow required for dose-based alignment. For this study, the dose-based alignment algorithm was implemented using MATLAB (version 7.12.0 [R2011a]; The MathWorks Inc., Natick, MA) as a plugin to CERR (Computational Environment for Radiotherapy Research, Washington University in St. Louis, St. Louis, MO)²⁴ and performed on an Intel Xeon X5680 3.33-GHz central processing unit (Santa Clara, CA). After we obtained the optimal setup position using each dose-based alignment methods, we imported the final isocenter information into the Eclipse proton treatment planning system (Varian Medical Systems, Inc., Palo Alto, CA) for final dose calculations, so we could compare the dose-based alignment with the anatomy-based alignment.

II.D. Statistical analysis

The statistical analysis focused on two sets of comparisons between the optimization methods: coverage of the target, and dose to normal tissue. For the first of these, we used the McNemar test to determine whether the methods significantly differed in meeting the target coverage constraint. For the second, we compared the changes in mean dose to the ipsilateral lung using a two-tailed paired t test with a 95% confidence interval. We performed our statistical analysis using GraphPad Prism (version 5.00 for Windows; GraphPad Software, San Diego, CA) and a p value less than 0.05 was considered statistically significant.

FIG. 2. Workflow diagram for the dose-based alignment method compared to the current IGRT workflow.

III. RESULTS

Seven of the 15 cases did not meet the target coverage constraint of $D_{99\%} \geq 95\%$ of the prescribed dose to the internal target volume when using the anatomy-based alignment. For five of these patients, the target $D_{99\%}$ dropped below 90% and two of these dropped below 66%. When applying isocenter corrections using the dose-based alignment shifts, we were able to recover the target dose for all seven of these patients ($p = 0.0156$) and meet the target coverage constraint. Table II lists the target (ITV) coverage and mean ipsilateral lung dose statistics for all 15 patients.

The dose-based method resulted in mean ipsilateral lung doses that were lower by an average of 2.74% of the prescribed dose, or 2.03 Gy for a prescribed dose of 74 Gy ($p = 0.0147$). The maximum decrease in mean ipsilateral lung dose was 11.0% of the prescribed dose. If considering only the eight cases in which the target constraint was met for both the anatomy-based and the dose-based alignment methods, the average decrease in mean ipsilateral lung dose was 4.5% ($p = 0.0083$), with decreases occurring in all but one case (patient 5).

Figure 3 shows a scatter plot and histogram of the vector magnitude differences of the isocenter shifts comparing the dose-based alignment to bony and internal gross tumor

TABLE II. Target (ITV) coverage requirement and mean ipsilateral lung dose.

Patient number	Target (ITV) $D_{99\%}$ ^a		Mean ipsilateral lung dose (% of prescribed dose)	
	Anatomy-based alignment (%)	Dose-based alignment (%)	Anatomy-based alignment	Dose-based alignment
1	99.4	96.8	45.3	38.4
2	95.3	100.5	51.5	40.5
3	80.5 ^a	95.8	40.3	34.0
4	93.8 ^a	97.0	61.8	60.2
5	98.2	98.9	21.0	21.7
6	96.9	96.6	54.1	52.5
7	100.4	96.2	42.9	38.3
8	97.7	97.2	53.3	49.0
9	101.1	98.8	38.3	35.0
10	87.5 ^a	96.7	39.2	42.2
11	80.2 ^a	95.6	58.9	61.7
12	94.4 ^a	96.7	47.4	46.3
13	65.7 ^a	95.7	76.1	73.1
14	57.2 ^a	95.7	45.2	46.2
15	100.4	95.8	51.0	46.1

^aDid not meet target constraint.

volume (iGTV) anatomy-based alignments, demonstrating that the dose-based alignment was not the same as either bony or iGTV anatomy-based alignments, and that the dose-based shifts did not cluster together toward any other observable anatomy.

Figure 4 shows DVHs for the target and the ipsilateral lung for patient 13, with separate results shown for the anatomy-based alignment and the dose-based alignment methods. In this case, the results of anatomy-based alignment did not meet our target coverage constraint while the results of the dose-based alignment methods met the constraint. In addition, after applying our optimized dose-based alignment shift, we reduced the mean dose to the ipsilateral lung by 2.3 Gy (3% of the prescription dose). Figure 5 shows the optimization trade-off between target coverage ($D_{99\%}$) and mean ipsilateral lung dose for all dose-based shifts evaluated in the search space.

The Pareto frontier, which shows the nondominating solutions for both the target coverage and normal tissue sparing, is shown as well as the dose-based shifts which satisfy the target coverage constraint and minimized normal tissue dose (green star). The dose distribution images overlaid on the CT for the same patient (patient 13) are shown in Fig. 6. When looking at the dose clouds, it is apparent that a much larger volume in the anatomy-based bony-alignment is underdosed when compared to the dose-based alignment. Interestingly, a lot of the underdosed regions fall near the center of the ITV and not out near the edges, likely due to overshooting of the posterior oblique beam, causing an underdosage in the proximal portion of the resulting spread out Bragg peak. For this patient, the $D_{99\%}$ improved from 65.7% up to 95.7% using our dose-based alignment.

IV. DISCUSSION

Image-guidance represents the latest development in radiation therapy. Although volumetric (CT-based) image guidance is popular in photon therapy, its deployment and full usage in proton therapy are still in the early stage. Due to the unique characteristics of proton dose distributions, image guidance alone may only solve a part of setup problems. It is important to note that proton compensators are designed with smearing margins in order to be robust to setup and motion errors, but do not account for anatomical changes during the course of treatment. Therefore, while the patient may be set up correctly based on anatomic landmarks, this may not be the most ideal setup based on the treatment time anatomy. Because proton dose distribution changes with changes in anatomy, the use of dosimetric objectives to set up a patient is perhaps more appropriate for proton therapy. Since our treatment goal is always dosimetric, a dose-based assessment is closer to our eventual goal, which makes our dose-based alignment viable in daily management of setup and range uncertainties. The method is based on the imperfect correction by the traditional anatomy/target alignment method. We assume the compensator and aperture will remain the same as in the original plan. Correction to the compensator and aperture will require daily

FIG. 3. Scatter plot and histogram of vector magnitude differences of the isocenter shifts comparing the dose-based alignments with the bony alignment and iGTV alignment.

FIG. 4. DVHs for the target (left) and ipsilateral lung (right) for patient 13. The anatomy-based and dose-based alignment DVHs are shown by the solid and dashed lines, respectively. The DVH bands show the extent of all of the dose calculations in the search space, with the lighter gray band corresponding to the calculated DVHs that did not meet the target coverage constraint and the darker gray bands showing the DVHs that did meet the constraint.

adaptive planning, which is not feasible in current technology or workflow. Our method is an intermediate step towards adaptive radiotherapy. It uses a simple isocenter shift, but the shift is based on dose calculation of the original plan applied to the daily anatomy. Therefore, it may be easier to deploy in clinical practice.

Our analysis is based on CT imaging acquired using the same scanner that is used for CT simulation. Full implementation of this method would require in-room or remote volumetric imaging resources with availability during pretreatment setup, a robust and accurate deformable image registration tool for propagation of contours, and available software at the treatment workstation for performing the dose-based alignment and subsequent review. During the treatment planning and verification stage, the physician would need to decide on organs-at-risk to monitor for dose-based alignment and action levels could be established to determine when a

physician review is necessary or a full adaptive replanning process needs to be triggered. Clinical application of our technique would likely utilize either a CT-on-rails system, remote patient positioning system,²⁵ or in-gantry cone-beam CT (CBCT) imaging. If a separate CT scanner is used, effort would need to be made to ensure that the CT calibration curve for conversion from CT number to relative linear stopping power is correct for the verification scanner. A CBCT system can be used if the CT numbers in the CBCT can be accurately corrected to match with the simulation CT or accurately calibrated for conversion to relative linear stopping power for proton dose calculation. A possible method for correcting these images for this purpose is to use deformable image registration to convert the CBCT to a “virtual CT” with CT number corrections, as described by Peroni *et al.*²⁶ and others.²⁷ These corrections would need to be accurate enough to be used in treatment planning to be feasible for use in this application.

As we saw from Table II, the $D_{99\%}$ target dose coverage dropped down to as low as 65.7% and 57.2% for two of the patients in our study when using bony anatomy to set up the patient. This is a very large dose decrease to the target resulting from the changes in heterogeneities in the patient which were not accounted for in the planning process. These types of errors could not be directly assessed if no dose information or periodic assessment of anatomy change was included. Fortunately, both of these patients received adaptive replans during the course of treatment due to the establishment of a weekly evaluation of the proton lung protocol patients. However, our results also indicate that a simple isocenter shift based on calculated dose distributions using treatment time CT images could be enough to correct for this drop in target dose coverage. This would allow us to correct it to an acceptable level without full-fledged adaptive replanning which will involve more resources. In addition, the dose-guided alignment could be used to indicate if a full adaptive replan is necessary based on the dosimetric analysis if the target coverage or normal tissue dose cannot be corrected to an acceptable level.

FIG. 5. An objective plot of the solution space of mean ipsilateral lung dose versus target $D_{99\%}$. Calculated solutions are shown in the dots, with the doses for anatomy-based and optimized single-isocenter dose-based alignments shown in the red (lower) and green (upper) stars, respectively. The target coverage constraint is shown by the green dashed line (above the line is meeting the constraint), and the Pareto frontier (nondominated solutions) is shown by the solid red lines.

FIG. 6. Dose distributions for patient 13 for the (a) plan and the last weekly CT based on (b) bony-alignment, and (c) dose-alignment. The dose clouds between 95% and 110% prescription dose levels for the bony-alignment and dose-alignment methods are also presented in axial, coronal, sagittal viewing planes to illustrate target coverage and locations of underdosage.

The accuracy of the algorithms employed for the dose-based alignment method is important to consider when defining action levels for correction or adaptive planning. The fast dose approximation method employed in this work⁷ has been found to be accurate for DVH calculations with an average and maximum root-mean-square deviation in DVH of 0.50% (average of 0.25% for the ipsilateral lung), which is sufficiently accurate for assessment of MLD. With smaller organs-at-risk that are close to high gradients, this accuracy will decrease, but even for the esophagus which is relatively small and was located right next to the high dose gradient, we found that the average RMS deviation in DVH was only 1.2% (maximum for any one case was 3.4% for shifts of up to 8 mm).

Our study and technique is only focused on correcting for interfractional anatomic changes, and currently does not address intrafractional changes due to patient movement or physiologic motion such as patient breathing. Any compensation for motion management is considered to have been accounted for in the treatment planning process. Additionally, while we examined lung patients for our study, this technique is not limited to lung treatments and could be applied to any anatomical site.

It is important to note that anatomy-based alignment may be sufficient in cases where anatomical changes are minimal. However, we have also shown that for cases in which the target coverage is acceptable even with anatomy-based alignment, dose-based alignment reduced dose to the normal tissue of the ipsilateral lung except in one case. This patient had the smallest tumor and the treatment therefore was the most sensitive to small differences in dose, especially near high-gradient regions. However, the resultant root mean square (and maximum) difference in DVH between the dose-based and anatomy-based alignment methods for this case was 1.0%

(2.1%), which is within the uncertainty of the fast dose approximation method⁷ and perhaps could be due to the search resolution used in this study (2 mm). While the average decrease in mean ipsilateral lung dose of 2.74% (~ 2 Gy) for all patients is seemingly small, this change is an appreciable dose reduction in the case of the ipsilateral lung due to its large absolute volume. The recent QUANTEC review for dose effects in the lung found that there was no suggested absolute safe MLD below which there is no pneumonitis, and reduction of risk for radiation pneumonitis is suggested to decrease by about 8% for a 2 Gy reduction based on a logistic regression fitted to multi-institutional data.²⁸

For this study, we evaluated only the dose to the target and one organ-at-risk (ipsilateral lung) to show that the methodology works. In general, any number of organs-at-risk can and should be incorporated into the objective function, and the optimal dose to normal tissues will be a tradeoff, in which case the optimal dose to normal tissues will necessarily require prioritizing/balancing the doses to each organ-at-risk. There are many ways to implement multicriteria optimization. In optimizing multiple criteria for dose-based alignment, a dose-volume-based single objective function similar to that implemented in treatment planning can be used. For each case, the user can select the objectives to reflect the best clinical scenario. For example, the dose to the spinal cord is generally an important objective that needs to be monitored. For patient 7, we noticed that the maximum dose to the spinal cord dose was above 45 Gy for both the anatomic and dose-based alignment setup positions. By adding equally weighted constraints to minimize the maximum dose to the spinal cord maximum dose and the mean dose to the esophagus, we were able to reduce the maximum dose to the spinal cord by 18 Gy to below 45 Gy and mean dose to the esophagus by 7 Gy but raising

the mean dose to the ipsilateral lung by 6 Gy. Depending on whether this increase dose to the lung is acceptable or not, decisions need to be made to reweight the optimization parameters to achieve the best clinical solution for the specific needs of the patient. The ultimate choice of the specific organs and weights to be included in the objective function should be left to the physician and depend on patient-specific acceptable target and normal tissue dose compromises. Depending on the optimization parameters selected, the dose-based alignment may potentially be the same as the anatomy-based alignment; however, unless dose-based evaluation is performed, there is no way to validate if the anatomy-based alignment is indeed the best solution.

Currently, we are using an exhaustive approach with discrete intervals since it allows us to demonstrate the concept because our current resources are powerful enough that we can calculate doses in about 7–15 min depending on the number of beams in the plan and the volume of the organs of interest. Ideally, total time for setup and imaging evaluation should take about 5–10 min or less. A refined optimization algorithm for determining search directions might improve the calculation speed. Computing time could also be greatly reduced by incorporating parallel computing. We could also take advantage of the fact that shifting the patient in a direction parallel to the beam axis (i.e., changing the air gap) does not change the proton dose distribution by much, thereby further reducing size of the search space.

Since anatomy change can affect the proton range from each individual beam differently, a beam-specific isocenter shift may potentially further improve the dose delivered to the patient. Additionally, individual field alignments may be applicable for multiroom facilities where prolonged waiting times between beams may be routinely observed. Ideally, this beam-specific isocenter shift would take into account the total dose from every beam in our optimization process. However, the search space is unacceptably large for a brute force search. For example, calculating the optimal shift for linked beams for a three-beam plan would require 729^3 or 387 420 498 combinations of beams. Even with all of the possible doses precalculated for each beam separately, calculating the objective function for all combinations of beams using our current methodology would take too long to be feasible for real-time application. We performed an initial study looking at performing a multiple isocenter shift using independent beam-specific dose optimization. We did this by looking at each beam separately and finding the isocenter shift that optimizes the dose to the target and the ipsilateral lung with the same parameters as our single isocenter dose-based optimization weighted by the relative beam-weighting in the treatment plan. It is important to point out that this multiple isocenter shift method makes sense only for proton delivery techniques in which each field is separately optimized to deliver uniform dose to fully cover the target. After this independent optimization, we looked at the resultant total dose delivered for each beam with the obtained isocenter shifts. In this study, we did not demonstrate the significant advantage of using the beam-specific isocenter shift method over the single-isocenter shift method. The mean ipsilateral lung doses for the single-

and multiple-isocenter shifts did not significantly differ ($p = 0.9464$). The multiple-isocenter dose-based method resulted in mean (max) ipsilateral lung doses that were lower by an average of 2.77% (11.0%) of the prescribed dose ($p = 0.0086$) compared to 2.74% (11.3%) of the prescribed dose for single-isocenter ($p = 0.0147$). While these doses are not significantly different, we can see that there is potential advantage to performing multiple-isocenter beam shifts to better optimize the dose that is delivered to the patient. We are currently investigating techniques to optimize full multiple-isocenter beam shifts with the total sum dose as the objective instead of simply using independent beam optimization.

V. CONCLUSION

We showed that because proton dose distribution changes with changes in anatomy in the beam path, a pure geometry-based target alignment is potentially insufficient for patient setup in proton therapy. On the other hand, we demonstrated that a dose-based patient setup was an effective image guidance approach for proton therapy. This particular approach improved target coverage and/or reduced dose to nearby normal tissue compared with the traditional anatomy-based image guidance approach based on our analysis of the dose to the ipsilateral lung. We proposed a unique approach to use a dose-based objective function to guide patient setup (i.e., isocenter adjustment), which bridges the gap between traditional image guided setup and the more complex adaptive radiotherapy. We showed that 7 of 15 plans did not meet the target coverage constraint when we used anatomy-based alignment. After we applied dose-based isocenter alignment, all met the target coverage constraint. The proposed dose-based alignment approach will also be useful as a trigger for adaptive radiotherapy when the dose-based simple isocenter shift method becomes inadequate to correct for more complicated dosimetric deviations in the treatment plan.

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^{a)} Author to whom correspondence should be addressed. Electronic mail: dong.lei@scrippshealth.org; Telephone: (858) 549-7526.

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