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Clinical Implementation of Intensity Modulated Proton Therapy for Thoracic Malignancies

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Abstract

Purpose—Intensity modulated proton therapy (IMPT) can improve dose conformality and better spare normal tissue over passive scattering techniques, but range uncertainties complicate its use, particularly for moving targets. We report our early experience with IMPT for thoracic malignancies in terms of motion analysis and management, plan optimization and robustness, and quality assurance.

Methods and Materials—Thirty-four consecutive patients with lung/mediastinal cancers received IMPT to a median 66 Gy(RBE). All patients were able to undergo definitive radiation therapy. IMPT was used when the treating physician judged that IMPT conferred a dosimetric advantage; all patients had minimal tumor motion (<5 mm) and underwent individualized tumor-motion dose-uncertainty analysis and 4-dimensional (4D) computed tomographic (CT)-based treatment simulation and motion analysis. Plan robustness was optimized by using a worst-case scenario method. All patients had 4D CT repeated simulation during treatment.

Results—IMPT produced lower mean lung dose (MLD), lung V₅ and V₂₀, heart V₄₀, and esophageal V₆₀ than did IMRT ($P < .05$) and lower MLD, lung V₂₀, and esophageal V₆₀ than did passive scattering proton therapy (PSPT) ($P < .05$). D₅ to the gross tumor volume and clinical target volume was higher with IMPT than with intensity modulated radiation therapy or PSPT ($P < .05$). All cases were analyzed for beam-angle-specific motion, water-equivalent thickness, and robustness. Beam angles were chosen to minimize the effect of respiratory motion and avoid previously treated regions, and the maximum deviation from the nominal dose-volume histogram values was kept at <5% for the target dose and met the normal tissue constraints under a worst-case scenario. Patient-specific quality assurance measurements showed that a median 99% (range,

95% to 100%) of the pixels met the 3% dose/3 mm distance criteria for the γ index. Adaptive replanning was used for 9 patients (26.5%).

Conclusions—IMPT using 4D CT-based planning, motion management, and optimization was implemented successfully and met our quality assurance parameters for treating challenging thoracic cancers.

Introduction

Proton therapy for lung cancer may be better able to spare critical structures than intensity modulated photon radiation therapy (IMRT) (1–6). Passive scattering proton therapy (PSPT), however, relies on 3-dimensional treatment planning (with its inherent limitations) and requires typically 0.5 to 1 cm smearing plus other uncertainty margins (7). The ability of PSPT to minimize lung V_{20} , mean lung dose (MLD), or mean esophageal dose may not be evident when tumors are located in complex anatomic positions or curve around critical structures. In such cases, compromised dose coverage must be considered to avoid damaging critical normal tissue structures.

In contrast to PSPT, intensity-modulated proton therapy (IMPT) that is based on scanning beam technology can simultaneously optimize the intensities and the energies of all pencil beams by using an objective function that accounts for targets and for constraints on normal tissues. Dosimetric studies indicated that IMPT might reduce the dose to the critical normal tissues relative to IMRT and allow individualized radical radiation therapy for stage III and stage I non–small cell lung cancer (NSCLC) in clinically challenging cases (8, 9). However, uncertainties with regard to proton range, tumor motion, and other aspects of treatment planning, treatment optimization, and quality assurance for IMPT are much more challenging and complex than those for PSPT or IMRT (10–14). At this time, 2 crucial scientific questions need to be addressed: (1) whether and how IMPT technology can be safely implemented in clinical settings for thoracic cancers; and (2) whether the physical advantages of IMPT can translate into improved clinical outcomes. Here we addressed the first scientific question. To the best of our knowledge, this is the first report on the clinical implementation of IMPT for thoracic cancers.

Methods and Materials

Patient selection

We analyzed all consecutive 34 patients who had been treated with IMPT from January 2011 to October 2013 for lung or other thoracic cancers or for recurrent disease that had been treated with thoracic radiation therapy or surgery. All patients had given written consent to be part of a prospectively maintained protocol database approved by an institutional review board. Disease had been staged in all cases with PET/CT and brain scanning to rule out meta-static disease. Selection for receipt of IMPT and inclusion in this study required the following: ability to undergo definitive radiation therapy with curative intent; performance status ≤ 2 ; no clear evidence of distant metastasis; minimal tumor motion (< 5 mm) during respiration; availability of findings from patient-specific, tumor-motion-related dose uncertainty analysis; availability of treatment simulation plans for

IMRT, PSPT, single-field optimized (SFO) IMPT, multifield-optimized with robustness constraints (MFO) IMPT, and analysis of those plans for robustness; and evidence of significant dosimetric advantage as judged by the treating physician for IMPT over IMRT or PSPT. Typically, better sparing of lung and/or esophagus or re-irradiation is the main reason that IMPT was chosen. Owing to the limited capacity of our proton scanning beam gantry, most of our patients who also met above criteria were treated with PSPT or IMRT. A flow chart of these procedures is shown in Figure 1.

Treatment simulation

All patients underwent 4-dimensional (4D) CT-based treatment simulation to document tumor motion as described previously (3, 4, 15, 16). The internal gross tumor volume (IGTV) was generated by using either a union of all GTV respiratory phases or an outline of the maximum intensity CT data as verified through different breathing phases. The clinical target volume (CTV) was defined as an 8-mm isotropic expansion of the IGTV and edited clinically based on pattern of tumor spreading and anatomic boundaries such as vertebral body, chest wall and heart and etc. The planning target volume (PTV), defined as an expansion of the CTV by 5 mm, was used for IMRT planning/evaluation and also used for proton plan evaluation. Plans were evaluated by using a CTV that had been generated from the GTV with the same (edited) expansions on individual phases (eg GTV_T50, CTV_T50). All normal structures were contoured on time-averaged CT scans. A PSPT plan with 2 or 3 fields was generated for each patient as described previously (2–4). SFO IMPT plans were then generated by using the Eclipse treatment planning system (version 8.9; Varian Medical Systems), and MFO IMPT plans with robustness constraints were generated by using in-house optimization software (12, 17, 18), with the final dose calculation performed by the Eclipse system. An averaged 4D CT set with an IGTV density override (ie assignment of maximum CT Hounsfield unit number from individual respiratory phases) (19) was used to create all PSPT, SFO IMPT, and MFO IMPT plans. Next, we created 2 “verification” dose distributions by recalculating the dose on the 4D simulation CT scans at 3 extreme breathing phases (T0 and T50) on the original plans. We then adjusted the original plan until the verification and original dose distributions all met the required prescription criteria including >95% CTV coverage and normal tissue dose volume constraints.

Patient-specific tumor-motion and related water-equivalent thickness analyses and beam angle selection

The 4D CT images were used to assess tumor motion in all directions (16, 20). For proton therapy, the dosimetric impact of tumor motion is a complex function involving respiratory and interfraction motion, the treatment plan, and the delivery system, including the scanning time and spot size, and fractionation, among other factors (14, 20, 21). Potential effects of intrafractional motion on the treatment plan were assessed by analyzing the motion both perpendicular (in-plane motion) and parallel (water-equivalent thickness, WET) to the beam axis. The WET analysis method, first proposed by Mori et al, (22), involves using changes in the WET within the IGTV between the different respiration phases to assess the influence of motion as follows. On the 4D CT simulation scans, the maximum inhale (T0) and maximum exhale (T50) phases were registered by using in-house deformable image registration software. The deformation vectors of voxels contained in the ICTV were used to

calculate the mean distance traveled by the tissue in the direction that is both perpendicular and parallel to the beam axis. Our limit was that 80% or more of the voxels in the ICTV that travel in the direction perpendicular to the beam axis should travel no more than 5 mm. Tissue density perturbation was also measured as follows. The difference in WET between T0 and T50 was calculated by retracing along the beam path from the patient's skin to the distal surface of the ICTV. In this analysis, the WET of each pixel in ICTV was calculated for the specific beam angle, and the corresponding differences of WETs resulting from respiration were quantified as a function of the beam angle. In our practice, the beam angles to be tested range from 0° to 360° in 30° increments. The percentage of the voxels in the ICTV in which the WET differences are not more than 5 mm ($S_{5\text{mm}}$) is used to make the final decision; our limit was that beam angles with $S_{5\text{mm}} \geq 80\%$ were acceptable. These results would also be used as part of the beam angle selection process. Consideration of beam proton beam path length, previous irradiation (if applicable), patient anatomy, and the WET and motion analysis were used to select beam angles for a given patient by using an iterative process. For patients who had previously received radiation, we sought to reduce the risk of severe side effects by choosing beam angles to pass through non-functional or fibrotic lung and to avoid previously irradiated esophagus, spinal cord, and skin.

Robust optimization

A robust optimization method for IMPT based on worst-case scenarios, first introduced by Lomax et al, was incorporated in our in-house treatment planning software for creating MFO IMPT plans (17, 18). For treating thoracic cancer with IMPT, the worst-case dose distribution is calculated as follows. For any given beam arrangement, we computed 9 different dose scenarios simultaneously: the nominal dose distribution (ie that with no consideration of uncertainties) and dose distributions incorporating (1) set-up uncertainties, obtained by shifting the isocenter of the CT images by ± 3 mm along the anterior-posterior, left-right, and superior-inferior directions (yielding 6 dose distributions); and (2) range uncertainty, by scaling the relative stopping power ratios to water by $\pm 3.5\%$ (yielding additional 2 dose distributions). The introduced errors (3 mm/3.5%) were systematic; according to the margin algorithm of Van Herk et al (23), systematic error of 3 mm in all directions can be translated into a 7.5-mm PTV. The worst-case dose distribution is then represented by the minimum of the 9 doses in each voxel in the ITV and the maximum of the 9 doses in each voxel outside the ITV. Accordingly, evaluations of plan robustness based on the worst-case dose-calculating approach as just described were used to evaluate the treatment plans. For lung cancer cases, we considered a difference of $\leq 5\%$ between the worst-case dose distribution and the nominal dose to be acceptable. If the plan was found to be not robust (quantified by a $>5\%$ difference), then the plans were reoptimized.

Quality assurance and adaptive planning

Patient-specific quality assurance measurements were done with a 2-dimensional (2D) ion chamber matrix for scanning beam treatment plans as previously described (21). The planned and measured 2D dose distributions were compared by using the γ -index (24) with a passing requirement of at least 90% of the pixels satisfying 3% dose or 3-mm distance to agreement criteria. The γ -index, which is commonly used for IMRT and IMPT quality assurance (21, 24, 25), calculates the minimum Euclidean distance in the normalized dose-

distance space and quantifies the difference between 2 dose distributions. All patients underwent repeated 4D CT simulation, either weekly or after 2 to 3 weeks of treatment, during treatment to determine whether adaptive replanning was needed to maintain target coverage ($>95\%$ for CTV) and to avoid overdosing critical structures (4) (Fig. 1). The plan was recalculated on the repeated 4D CT scans. Contours were deformed from the planning CT to repeated CT, and the treating physician reviewed the new contours and dose-volume histograms. If an adaptive plan was deemed necessary, the plan would be developed using robust optimization as described earlier, and the same patient-specific quality assurance process would be done before treatment.

Results

Dosimetric comparisons among IMPT, IMRT, and PSPT plans and clinical indications

The characteristics of the 34 patients in this study are shown in Table 1. For all patients tested, IMPT plans were associated with lower MLD, lung V_5 and V_{20} , heart V_{40} , and esophageal V_{60} values than were IMRT plans ($P<.05$) and lower MLD, lung V_{20} , and esophageal V_{60} than PSPT plans ($P<.05$) (Fig. 2A). No differences were found between IMPT and IMRT or PSPT in D_{95} (the dose given to 95% of a given volume) to the GTV or CTV, but IMPT had a slightly higher D_5 to the GTV and CTV compared with IMRT or PSPT ($P<.05$). PSPT produced the highest esophageal V_{60} in these clinically challenging cases. For most of these patients, IMPT was the only option for treatment because of the need for normal tissue sparing. Typically, IMPT was chosen because of a significant dosimetric advantage over other modalities (Fig. 2B) or because it was the only option for definitive treatment to spare spinal cord, esophagus, and lung (Fig. 2C), or because of recurrent disease that had been treated previously with radiation therapy (Fig. 2D).

Analyses of tumor motion, WET, beam angle selection, and plan robustness

Beam angle-specific tumor motion and WET analyses were performed for each patient as described in Methods. The absolute WETs of the pixels within the ITV for every tested beam angle were calculated on T0 and T50 phases. The WETs of the pixels on the distal surface of the ITV orthogonal to the beam (beam angle = 0) were projected to a plane and shown as a 2D map (Fig. 3). Figure 3A shows the WET change between T0 and T50 as a function of incident proton beam angle, and Figure 3B shows an example of the same patient at a beam angle of 160° . The $S_{5\text{mm}}$ for this beam angle was 95.1%. Optimal beam angles that minimized the effect of respiratory motion were then selected based on these analyses. Findings from patient-specific tumor motion and WET analyses are summarized in Table 2. The data showed a median 86.2% of the voxels in the IGTV that traveled in perpendicular to the beam axis by 5 mm. The data also met our acceptability limit of 80% of the voxels in the ITV in which the WET differences are not more than 5 mm ($S_{5\text{mm}}$).

The results of a robustness analysis of an MFO IMPT plan for a representative patient are shown in Figure 4. The maximum deviation from the nominal dose-volume histogram should be $<5\%$ for the target dose and should meet the normal tissue constraints under the worst-case scenario for the plan to be approved. These findings, plus the results of

robustness analyses for all patients (Table 2), indicate that all plans met the criteria for approval.

Quality assurance and adaptive replanning

Quality assurance results for all patients are summarized in Table 2. In all 2D ion-chamber measurements, more than 99% of the pixels (range, 95% to 100%) met the 3% dose/3-mm distance criteria for the γ -index. All 34 patients received 1 to 7 repeated CTs during radiation therapy. Verification plans were generated for each of these repeated CTs and were reviewed by the treating physicians. Adaptive replanning was used for 9 patients (26.5%) and involved the same criteria as reported previously (4). Replanning was required for 7 of these patients because of treatment-related changes that led to <95% coverage of the CTV or GTV; the other 2 patients required replanning to avoid overdoing critical normal tissues as judged by the treating physicians. The median time at which plans were modified was after 10 fractions (range, 5 to 25 fractions). Adaptive IMPT plans were usually begun by 3 working days after the resimulation.

Discussion

Our results suggest that the improved normal tissue sparing afforded by IMPT makes IMPT the treatment option of choice for all of the patients in this study, who had either tumors in anatomically complex locations or had previously received thoracic radiation. For other patients who had IMPT, PSPT, and IMRT comparison plans but were not treated with IMPT because of the limited capacity of our scanning beam gantry or insurance issues, IMPT is always better or similar to spare critical normal structures (data not shown). Our 4D CT-based tumor motion analysis and management with IMPT robustness optimization achieved our goals of keeping patient-specific quality assurance measurements, with a median 99% of the pixels meeting the 3% dose/3-mm distance criteria for the γ -index. These data, the first of their kind, indicate that IMPT treatment for thoracic cancer with tumor motion <5 mm is safe based on physics analysis using our current approach. Although longer follow-up time is needed before clinical outcomes can be formally reported, our preliminary results seem promising. With a median follow-up time of 6.5 months, 6 patients (18%) experienced grade 2 or 3 esophagitis, and 5 (15%) experienced grade 2 or 3 dyspnea. No patients manifested grade 4 or 5 toxicity of any type. Considering that most of these cases were technically quite challenging and that 12 patients had already received radiation therapy, the outcome is even better than our initial expectations. Our intent in this report is to share our firsthand physics and clinical experience so that more patients, particularly those who have no options for treatment because of intolerance of photon therapy, can benefit from this novel technology. A recent tumor motion study indicated that patients with thoracic tumors that move >5 mm could be treated safely, without compromising target coverage, by using conventional fractionation and dose-repainting techniques (26). However, clinical data with longer follow-up times are needed to validate our initial experience as reported here and to expand the clinical indications for tumor that move >5 mm for IMPT.

In proton therapy, unlike photon therapy, the range uncertainty originating from artifacts in the CT image or the conversion of Hounsfield units to stopping powers must be accounted

for because that uncertainty can change the proton dose distribution, which can result in target dose misses or overdoses to critical structures. Setup error and intrafractional organ motion not only cause geometric displacement of the tumors and normal tissues, which blurs the dose gradients from target volume to normal tissue, but also can affect tissue densities, which can alter the ranges of the Bragg peaks and lead to distorted dose distributions. The influence of these uncertainties becomes more significant in highly modulated IMPT plans because the individual fields can be quite inhomogeneous, and steep dose gradients can be located in the middle of the target; the concept of “safety margins” thus fails, to some extent, for IMPT. In addition, when beam scanning techniques are used to treat moving tumors, the dynamic pencil beam delivery and target motion lead to interference. This phenomenon, also referred to as the interplay effect, can cause additional deterioration of the delivered dose distribution, usually manifested in local underdosage and overdosage (10, 11, 14). Interfractional changes in anatomy and motion patterns arising from tumor shrinkage or body weight loss or gain further require regular monitoring and timely adjustment of treatment plans over time.

Several studies have shown that the use of repeated scanning and fractionated treatment can effectively reduce the impact of interplay by averaging out motion-caused effects and therefore lead to an acceptable target dosage (14, 20, 27). The irradiation time per spot in the beam delivery system used at our institution ranges from 1 to 10 milliseconds, which corresponds to the minimum allowed monitor unit (MU) (0.005) and maximum allowed MU (0.04). Thus, if a total MU >0.04 is required for a spot, the spot must be split and rescanning done as needed until all the MUs are delivered. However, this mechanical limit is helpful for alleviating interplay effects.

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References

1. Chang JY, Cox JD. Improving radiation conformality in the treatment of non-small cell lung cancer. *Semin Radiat Oncol.* 2010; 20:171–177. [PubMed: 20652085]
2. Chang JY, Zhang X, Wang X, et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in stage I or stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2006; 65:1087–1096. [PubMed: 16682145]
3. Chang JY, Komaki R, Lu C, et al. Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. *Cancer.* 2011; 117:4707–4713. [PubMed: 21437893]
4. Koay EJ, Lege D, Mohan R, et al. Adaptive/nonadaptive proton radiation planning and outcomes in a phase II trial for locally advanced non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2012; 84:1093–1100. [PubMed: 22543217]
5. Gomez DR, Gillin M, Liao Z, et al. Phase 1 study of dose escalation in hypofractionated proton beam therapy for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2013; 86:665–670. [PubMed: 23688815]

6. De Ruyscher D, Chang JY. Clinical controversies: Proton therapy for thoracic tumors. *Semin Radiat Oncol*. 2013; 23:115–119. [PubMed: 23473688]
7. Mohan R, Matney J, Bluett J, et al. IMRT versus passively scattered proton therapy (PSPT) for locally advanced NSCLC: impact of changing techniques and technologies over the course of a randomized trial (abstract). *Int J Radiat Oncol Biol Phys*. 2012; 84:S565–S566.
8. Zhang X, Li Y, Pan X, et al. Intensity-modulated proton therapy reduces the dose to normal tissue compared with intensity-modulated radiation therapy or passive scattering proton therapy and enables individualized radical radiotherapy for extensive stage IIIB non-small-cell lung cancer: A virtual clinical study. *Int J Radiat Oncol Biol Phys*. 2010; 77:357–366. [PubMed: 19660879]
9. Register SP, Zhang X, Mohan R, et al. Proton stereotactic body radiation therapy for clinically challenging cases of centrally and superiorly located stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2011; 80:1015–1022. [PubMed: 20615629]
10. Lomax AJ. Intensity modulated proton therapy and its sensitivity to treatment uncertainties 1: The potential effects of calculational uncertainties. *Phys Med Biol*. 2008; 53:1027–1042. [PubMed: 18263956]
11. 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*. 2008; 53:1043–1056. [PubMed: 18263957]
12. Liu W, Zhang X, Li Y, et al. Robust optimization of intensity modulated proton therapy. *Med Phys*. 2012; 39:1079–1091. [PubMed: 22320818]
13. Stuschke M, Kaiser A, Pottgen C, et al. Potentials of robust intensity modulated scanning proton plans for locally advanced lung cancer in comparison to intensity modulated photon plans. *Radiother Oncol*. 2012; 104:45–51. [PubMed: 22560714]
14. Grassberger C, Dowdell S, Lomax A, et al. Motion interplay as a function of patient parameters and spot size in spot scanning proton therapy for lung cancer. *Int J Radiat Oncol Biol Phys*. 2013; 86:380–386. [PubMed: 23462423]
15. Chang JY, Dong L, Liu H, et al. Image-guided radiation therapy for non-small cell lung cancer. *J Thorac Oncol*. 2008; 3:177–186. [PubMed: 18303441]
16. Liu HH, Balter P, Tutt T, et al. Assessing respiration-induced tumor motion and internal target volume using four-dimensional computed tomography for radiotherapy of lung cancer. *Int J Radiat Oncol Biol Phys*. 2007; 68:531–540. [PubMed: 17398035]
17. Liu W, Li Y, Li X, et al. Influence of robust optimization in intensity-modulated proton therapy with different dose delivery techniques. *Med Phys*. 2012; 39:3089–3101. [PubMed: 22755694]
18. Liu W, Frank SJ, Li X, et al. PTV-based IMPT optimization incorporating planning risk volumes vs robust optimization. *Med Phys*. 2013; 40:021709. [PubMed: 23387732]
19. Kang Y, Zhang X, Chang JY, et al. 4d proton treatment planning strategy for mobile lung tumors. *Int J Radiat Oncol Biol Phys*. 2007; 67:906–914. [PubMed: 17293240]
20. Li H, Li Y, Zhang X, et al. Dynamically accumulated dose and 4d accumulated dose for moving tumors. *Med Phys*. 2012; 39:7359–7367. [PubMed: 23231285]
21. Zhu XR, Poenisch F, Song X, et al. Patient-specific quality assurance for prostate cancer patients receiving spot scanning proton therapy using single-field uniform dose. *Int J Radiat Oncol Biol Phys*. 2011; 81:552–559. [PubMed: 21300457]
22. Mori S, Dong L, Starkschall G, et al. A serial 4DCT study to quantify range variations in charged particle radiotherapy of thoracic cancers. *J Radiat Res*. 2014; 55:309–319. [PubMed: 24142967]
23. van Herk M, Remeijer P, Rasch C, et al. The probability of correct target dosage: Dose-population histograms for deriving treatment margins in radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000; 47:1121–1135. [PubMed: 10863086]
24. Low DA, Harms WB, Mutic S, et al. A technique for the quantitative evaluation of dose distributions. *Med Phys*. 1998; 25:656–661. [PubMed: 9608475]
25. Ezzell GA, Burmeister JW, Dogan N, et al. IMRT commissioning: Multiple institution planning and dosimetry comparisons, a report from AAPM Task Group 119. *Med Phys*. 2009; 36:5359–5373. [PubMed: 19994544]
26. Li Y, Kardar L, Li X, et al. On the interplan effects with proton scanning beams in stage III lung cancer. *Med Phys*. 2014; 41:021721. [PubMed: 24506612]

27. Schätti A, Zakova M, Meer D, et al. Experimental verification of motion mitigation of discrete proton spot scanning by re-scanning. *Phys Med Biol*. 2013; 58:8555–8572. [PubMed: 24254249]

Summary

Intensity modulated proton therapy (IMPT) can offer improved dose conformality but also has increased uncertainties, particularly when used to treat moving targets. We report here our preliminary experience with the clinical implementation of IMPT for thoracic cancer and describe clinical indications, motion analysis and management, plan optimization and robustness analysis, and quality assurance. Our data indicate that IMPT treatment for thoracic cancer with tumor motion <5 mm is safe with use of the approach developed at our institution.

Fig. 1.

Procedural flow chart for intensity modulated proton therapy (IMPT) quality assurance. 4D CT = 4-dimensional computed tomography; MFO = multifield optimization; SFO = single-field optimization.

Fig. 2.

(A) Comparison of dosimetric variables for intensity modulated proton therapy (IMPT), passive scattering proton therapy (PSPT), and intensity modulated radiation therapy (IMRT). Values shown are means of all patients. (B) Comparisons of dose-volume histogram (DVH), isodose distributions, and total mean lung dose for a representative patient who received chemotherapy with IMPT to 74 Gy(RBE) for stage III NSCLC. (C) Scans and DVHs for a patient with bulky stage III non-small cell lung cancer who had received urgent palliative photon therapy (30 Gy in 10 fractions using anterior/posterior fields, with spinal cord and esophagus receiving 30 Gy) followed by IMPT to 60 Gy in 30 fractions. The lesion could not be treated definitively with IMRT (because of a cumulative lung V5 >85%, not shown) or PSPT (significant amounts of esophagus would have received a cumulative dose of 80 to 90 Gy, not shown). (D) Scans and DVHs for a patient who had received photon therapy (60 Gy in 30 fractions) for small cell lung cancer, followed by IMPT to 45 Gy in 30 fractions twice a day with chemotherapy for an in-field recurrence. AP

= anteroposterior; CTV = clinical target volume; GTV = gross tumor volume; MLD = mean lung dose; PA = posteroanterior; PET = positron emission tomography; RT = radiation therapy; Vx, volume of the cited organ (%) exposed to the indicated dose [in Gy(RBE)].

Fig. 3.

Water-equivalent thickness (WET) analysis and beam angle selection. (A) Mean values of WET variation of the pixels in IGTV plotted as a function of beam angles. (B) WET analysis of a given beam angle of 160° , chosen based on minimal WET variation as shown in (A) along with tumor location for internal gross tumor volume (IGTV), with distal pixels calculated on reference (T0) and target (T50) phase scans; the difference between scans is shown as T50 minus T0. Histogram illustrates the percent volume differences in WET in the pixels within the IGTV was <5 mm (red vertical lines indicate S_{5mm}). (C) Percentages of the voxels in IGTV with WET differences <5 mm (S_{5mm}) are plotted as a function of beam

angle. The chosen 160° beam angle was confirmed as being within the acceptability limit of 80%. A color version of this figure is available at www.redjournal.org.

Fig. 4.

Robustness analysis of an intensity modulated proton therapy plan. Solid lines indicate nominal dose-volume histogram calculated from the time-averaged computed tomographic scan; dotted lines indicate DVH calculated from the iso- or relative stopping power ratios shifted 9 scenarios. GTV = gross tumor volume; ITV = internal tumor volume.

Table 1

Patient characteristics

Characteristic	No. of patients (%)	
Sex		
Male	16 (47)	
Female	18 (53)	
Age, y, median (range)	67 (40–82)	
Pulmonary tumor location		
	Without lymph nodes	With lymph nodes
RUL	5 (14.7)	2 (5.9)
RLL	3 (8.8)	1 (2.9)
LUL	5 (14.7)	1 (2.9)
LLL	1 (2.9)	0
Right hilum	2 (5.9)	1 (2.9)
Right main bronchus	0	1 (2.9)
Left hilum	1 (2.9)	0
Left main bronchus	1 (2.9)	1 (2.9)
Anterior mediastinum	1 (2.9)	0
Right hemithorax	1 (2.9)	0
Mediastinal lymph nodes only		5 (14.7)
Both mediastinal and supraclavicular nodes		2 (5.9)
Tumor histology		
Adenocarcinoma	15 (44)	
Squamous cell carcinoma	10 (29)	
NSCLC or not otherwise specified	2 (6)	
Small cell carcinoma	1 (3)	
Large cell neuroendocrine carcinoma	1 (3)	
Other thoracic malignancies	5 (15)	
Disease type		
Primary*	22 (65)	
Recurrence	12 (35)	
Previous radiation to chest	11 (32)	
Previous radiation dose, median (range)	60 (30–70)	
GTV volume, cm ³ , median (range)	65 (2.3–1692.1)	
CTV volume, cm ³ , median (range)	239 (23.4–2449)	
Proton radiation dose, Gy (RBE) (range)	66 (45–78)	
Disease stage of primary lung cancer (n=20)		
I	1 (5)	
II	1 (5)	
III	17 (85)	
IV (isolated brain metastasis)	1 (5)	

Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; LLL = left lower lobe; LUL = left upper lobe; NSCLC = non-small cell lung cancer; RLL = right lower lobe; RML = right middle lobe; RUL = right upper lobe.

*
20 non-small cell lung cancer, 2 other cancers.

Table 2

Motion analysis, robustness analysis, and quality assurance results for all patients

Variables	Values
Motion analysis	
In-plane (perpendicular to beam axis) motion of GTV center, mm, median (range)	3.6 (2.1–5.6)
WET change between T0 and T50, mm, median (range)	4.1 (0.5–5.1)
Field-specific S_{5mm} , %, median (range)	86.2 (78.5–100)
Worst-case robustness analysis: deviation from nominal dose	
Lung V_5 , % (SD)	3.1 (1.4)
Lung V_{20} , % (SD)	2.5 (1.0)
Mean lung dose, Gy (SD)	1.8 (0.7)
Esophagus V_{60} , % (SD)	3.9 (4)
Heart V_{40} , % (SD)	2.2 (1.9)
GTV D_5 , D_{95} , Gy (SD)	1.4, 1.7 (0.6, 0.6)
ITV D_5 , D_{95} , Gy (SD)	1.6, 3.2 (0.8, 1.5)
Quality assurance	
γ -index with 3 mm/3% criteria, %, mean (range)	99.37 (94.54–100)

Abbreviations: Dx = dose [in Gy(RBE)] to x% of the cited volume; GTV = gross tumor volume; ITV = internal target volume; SD = standard deviation; V_x , volume of the cited organ (%) exposed to the indicated dose [in Gy(RBE)]; WET = water-equivalent thickness.