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Impact of Respiratory Motion on Worst-Case-Scenario Optimized Intensity-Modulated Proton Therapy for Lung Cancers

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Abstract

Background—We compared conventionally optimized intensity-modulated proton therapy (IMPT) treatment plans against the worst-case scenario optimized treatment plans for lung cancer. The comparison of the two IMPT optimization strategies focused on the resulting plans' ability to retain dose objectives under the influence of patient set-up, inherent proton range uncertainty, and dose perturbation caused by respiratory motion.

Methods—For each of the 9 lung cancer cases two treatment plans were created accounting for treatment uncertainties in two different ways: the first used the conventional method: delivery of prescribed dose to the planning target volume (PTV) that is geometrically expanded from the internal target volume (ITV). The second employed the worst-case scenario optimization scheme

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Conflicts of Interest Notification

None

that addressed set-up and range uncertainties through beamlet optimization. The plan optimality and plan robustness were calculated and compared. Furthermore, the effects on dose distributions of the changes in patient anatomy due to respiratory motion was investigated for both strategies by comparing the corresponding plan evaluation metrics at the end-inspiration and end-expiration phase and absolute differences between these phases. The mean plan evaluation metrics of the two groups were compared using two-sided paired *t*-tests.

Results—Without respiratory motion considered, we affirmed that worst-case scenario optimization is superior to PTV-based conventional optimization in terms of plan robustness and optimality. With respiratory motion considered, worst-case-scenario optimization still achieved more robust dose distributions to respiratory motion for targets and comparable or even better plan optimality [D_{95%} ITV: 96.6% versus 96.1% ($p=0.26$), D_{5%} – D_{95%} ITV: 10.0% versus 12.3% ($p=0.082$), D_{1%} spinal cord: 31.8% versus 36.5% ($p=0.035$)].

Conclusions—Worst-case scenario optimization led to superior solutions for lung IMPT. Despite of the fact that worst-case-scenario optimization did not explicitly account for respiratory motion it produced motion-resistant treatment plans. However, further research is needed to incorporate respiratory motion into IMPT robust optimization.

Keywords

intensity-modulated proton therapy; lung cancer; respiratory motion; robust optimization; root-mean-square dose; treatment planning

I. INTRODUCTION

Most proton treatments for lung cancer have been delivered using passive scattering proton therapy (PSPT), in which broad beams are shaped to conform to the target volume using customized apertures and compensators. In contrast, scanning beam proton therapy uses magnetic steering of a narrow proton beam (beamlet) to deliver a dose to a specifically located spot (i.e., a beamlet). By modulating the weight of individual beamlets, intensity-modulated proton therapy (IMPT) offers the same high-dose conformity as intensity-modulated x-ray therapy and better sparing in the mid-to-low dose range.(1, 2)

Several factors, however, are known to distort dose distribution in proton therapy for lung cancer. Intra-fractional motion may cause considerable changes in patient geometry and, consequently, in dose distributions.(3–5) The interplay effect of dynamic delivery and tumor motion has been reported to degrade the quality of the resulting dose distribution, particularly in IMPT.(3, 6–12) In order to account for respiratory motion, an internal gross target volume (IGTV) is generally formed to encompass the extent of gross target volume (GTV) motion in all phases using four-dimensional computed tomography (4D CT). The IGTV is then expanded to form internal target volume (ITV) by an additional margin (in the case of this study 8 mm) to account for subclinical microscopic disease. Techniques such as breath-hold, gating, and tumor tracking can be used to mitigate the effects of more substantial respiratory motion. In addition, the change in tissue density due to respiratory motion was generally accounted for by the use of averaged 4D CT and integrated GTV (over

all phases) density override. Kang *et al* (13) demonstrated that this method was effective in preserving target coverage under the influence of respiratory motion for PSPT.

In addition to respiratory motion, the presence of heterogeneous tissue consisting of the lung, ribs, and soft tissue can make IMPT vulnerable to patient set-up and range uncertainties as the range of protons is a function of tissue density along the beam path.(5) Patient set-up uncertainties can occur throughout the course of simulation and daily treatment. Sources of range uncertainty include tumor shrinkage, weight change, and CT number and stopping power ratio uncertainties. Unlike uncertainties caused by respiratory motion, patient set-up and range uncertainties include systematic uncertainties that can affect the delivery of an intended dose throughout the course of fractionated treatment. The IMPT plan's integrity under set-up and range uncertainties must be considered, regardless of motion, especially for tumors in a highly heterogeneous region, as are typically found in lung cancer cases.

Conventionally, a safety margin (in the case of this study 5 mm) can be assigned around ITV to form a planning target volume (PTV)(14) to handle the patient set-up uncertainty. Recently, a few robust optimization techniques have been reported to be effective in compensating for set-up and range uncertainties in IMPT planning.(15–21) However, the robust optimization methods reported in the literature (15–21) do either not perform a patient population study or not evaluate the impact of respiratory motion upon the quality of plans derived by robust optimization. Therefore, it is necessary to investigate the efficacy of the worst-case scenario optimization planning strategy for lung cancer in a patient population and then to evaluate the impact of dose variation arising from respiratory motion on the quality of plans derived from the worst-case scenario optimization. These effects have not been previously studied in one study.

This paper represents our efforts to study the combined influence of set-up uncertainty, range uncertainty, and respiratory motion on IMPT for lung cancer. We hypothesize that, even though worst-case scenario optimization does not directly account for respiratory motion, it can achieve better plan quality, under the influence of respiratory motion, than the conventionally optimized plan, since the worst-case scenario optimized plan is less sensitive to the perturbation of tissue density in general. Here, we present a comparison of the results at first without respiratory motion considered. We then go a step further and perform a robustness evaluation to compare the two planning methods, with respiratory motion considered, to see the impact of the dose variation arising from respiratory motion on the quality of the plans.

II. METHODS AND MATERIALS

A. Patient data and treatment planning

We randomly selected and retrospectively evaluated the treatment plans for 9 lung cancer patients (Supplemental Table 1) who had been treated with PSPT at XXXX and replanned them using IMPT. The patients included in this work were on an institutional protocol, which required that the tumor motion was less than 10 mm in order to minimize the influence of respiratory motion. Two treatment plans were created, for each patient with

identical dosimetric goals using our in-house developed treatment planning system.(19) For the conventional planning strategy, the PTV was formed by isotropically expanding the ITV by 5 mm to account for set-up uncertainties only.(14, 22)

For the worst-case scenario optimization, the inter-fractional patient set-up uncertainties were simulated by shifting the isocenter of the patient in the antero-posterior (AP), superior-inferior (SI), and lateral (RL) directions by the same margin as was used for defining the PTV, yielding six dose distributions and the corresponding “influence matrices” (i.e., beamlet dose distributions per unit intensity) by recalculating the corresponding dose distributions. Range uncertainties were simulated by scaling the stopping power ratios by $\pm 3.5\%$ (14, 22) to generate two additional dose distributions and influence matrices corresponding to minimum and maximum proton ranges, respectively, by recalculating the corresponding dose distributions. We derived the worst-case dose distribution by choosing the smallest dose among the nine doses (8 perturbed dose distribution plus the nominal dose distribution) for each voxel in the ITV and the largest dose for each voxel outside the ITV. (23) The advantage of this method is that fewer calculations are needed and a detailed model of uncertainties is not required compared to the probabilistic method (24). Recently Casiraghi et al (24) reported that a simplified definition of worst-case dose distribution as stated above represents the worst case plan overall, although individual voxel doses could still be worse for other plans. We then used this worst-case dose distribution to compute the objective function value for a given iteration. For worst-case scenario optimization, we used a standard quadratic objective function:

$$F(\omega_j) = \sum_{i \in \text{ITV}} p_{\text{ITV}, \min} (D_{i, \min} - D_{0, \text{ITV}})^2 + \sum_{i \in \text{ITV}} p_{\text{ITV}, \max} (D_{i, \max} - D_{0, \text{ITV}})^2 + \sum_{i \in \text{OARS}} p_{\text{OARS}} H(D_i - D_{0, \text{OARS}}) (D_{i, \max} - D_{0, \text{OARS}})^2 \quad (1)$$

where p denotes the penalty weight of the corresponding term and D_0 denotes the prescribed dose for the corresponding organ. The Heaviside function, $H(D_i - D_0)$, is defined conventionally (i.e., its value is unity if $D_i > D_0$ and zero if $D_i \leq D_0$). The terms

$D_{i, \min} = \min_m \{D_i^m\}$ and $D_{i, \max} = \max_m \{D_i^m\}$ in Eq. (1), and they respectively indicate the minimum and maximum dose among the m possible doses D_i^m in voxel i ($m=9$ here), which

are calculated using $D_i^m = \sum_j \text{IM}_{i,j}^m \omega_j^2$ in each iteration, where IM is the influence matrix and ω^2 is the fluence map. The m IMs $\text{IM}_{i,j}^m$, incorporating range and setup uncertainties, were pre-calculated using an in-house dose calculation engine for proton pencil beams of a finite size (25) as mentioned before and stored in local memory for efficient optimization. We further constrained the target dose inhomogeneity in the objective function (the underlined term). The beamlet weights were optimized to deliver the prescribed dose directly to the ITV.

The number of spots and their positions before optimization were the same for both PTV-based and worst-case scenario optimization (Supplemental Table 2). The dose under the nominal scenario for all plans was checked to ensure that the institutional dose-volume constraints were met (Supplemental Table 3).

B. Plan robustness and plan quality evaluation without respiratory motion considered

We compared the plan robustness from PTV-based optimization with that from worst-case scenario optimization using the root-mean-square dose deviation (RMSD) volume histogram (RVH) (26, 27). Both set-up and range uncertainties were considered in the plan robustness evaluation, although the combined uncertainties were not considered. The RVH (Figure 1) captured the overall effect of uncertainties on the dose to a volume of interest analogous to the dose-volume histogram (DVH) assessing nominal dose. The area under the RVH curve (AUC) gave a single numerical measure of the plan's robustness for a given volume of interest. The smaller the AUC, the more robust the plan was for structures between competing plans. A case with combined uncertainties is shown in Figure 1 to demonstrate the efficacy of the method in the presence of both set-up and range uncertainty.

$D_{95\%}$, the dose covering 95% of the structure's volume, and the $D_{5\%}$, the dose covering 5% of the structure's volume, were derived from the target DVH. $D_{95\%}$ and $D_{5\%} - D_{95\%}$ were used to assess target dose coverage and homogeneity. The values were then normalized to the corresponding prescription doses. The dose covering a percentage of the structure's volume ($D_{\%}$) was calculated and compared for organ-at-risks (OARs). We used $D_{1\%}$ dose for spinal cord and brachial plexus, $D_{33\%}$ dose for esophagus and heart, and $D_{67\%}$ dose for esophagus. In addition, we used the mean dose (D_{mean}) and the normalized volume receiving 20 Gy (V_{20}) for the total lung volume.

D. Evaluation of the impact of range uncertainties arising from respiratory motion

For each patient, the dose distributions were recalculated at two respiratory phases (end-inspiration and end-expiration) of the simulation 4D CT. The worst-case dose distribution (23) described above was computed for each phase for both plans. DVHs were calculated in both the nominal and worst-case dose distributions for these two phases. The corresponding dose indices discussed in subsection II.B were derived in both the nominal and worst-case dose distributions for these two phases. The smaller one for $D_{95\%}$ and the larger ones for all other DVH dose indices between these two phases were used to assess the effect of respiratory motion on target dose coverage, target dose homogeneity, and normal tissue sparing at the two respiratory phases. The absolute differences of the corresponding DVH dose indices in both the nominal and worst-case dose distributions at these two phases were used to assess the effect of respiratory motion on plan robustness. Both the worst case dose distributions (the more conservative way of evaluating the dose distribution) and the nominal distribution (the standard clinical practice of evaluating the dose distribution) were computed for both plans, in order to give a more comprehensive picture.

In order to achieve sufficient statistics, we used a recently developed statistical technique (28) to evaluate the robustness of the IMPT plans for a subset of patients. In this statistical technique, 600 combinations of setup and range uncertainties were introduced to the CTs corresponding to end-inspiration and end-expiration phases for both the worst-case scenario optimized plan and PTV-based plan (in total 2,400 calculations per patient), and a fast dose calculation technique was used to calculate the dose distribution with the introduced uncertainties (29). DVHs of the target volumes and critical structures for each dose distribution were calculated and displayed in band graphs of 600 dose distributions

associated with the corresponding range and setup uncertainties. For convenience, the DVHs derived by choosing the nominal dose of a voxel were also displayed. Then the corresponding DVH indices were used to compare the plan quality and plan robustness under the influence of respiratory motion.

E. Statistical analysis

We performed a statistical comparison analysis of the results from both plans with and without respiratory motion considered. The means of AUCs and all DVH dose indices as mentioned before were calculated for all 9 cases. The data were compared with paired *t*-tests, or the Wilcoxon test if outliers existed, using SPSS 19.0 software (International Business Machines, Armonk, New York). A *p*-value of < 0.05 was considered statistically significant.

III. RESULTS

A. Plan robustness, target dose coverage, homogeneity, and normal tissue sparing without accounting for respiratory motion

Figure 2 depicts the transverse dose distributions for an axial CT slice for one of the nine patients with conventional optimization on the left and worst-case scenario optimization on the right. Dose distributions with the patient in the planned position on top, a 5-mm anterior shift in the middle, and 5 mm anterior shift combined with a 3.5% increase in range on the bottom are shown. Isodose lines in the conventionally optimized plan are perturbed to a greater degree than in the worst-case scenario optimized plan, both for the 5mm shift and the combination of 5mm shift and 3.5% increase in range, Figure 2 also demonstrates better spinal cord sparing for worst-case scenario planning, when set-up and range uncertainties are introduced.

The mean of the computed AUCs of the targets and OARs for the 9 lung cancer cases are shown in Table 1. Compared to conventional optimization, worst-case scenario optimization was significantly less affected by uncertainties for both targets and OARs (smaller areas for all structures). Except for the total lungs, heart, left lung, and brachial plexus, all end points had significantly smaller AUCs (*P* values < 0.05) with worst-case scenario optimization than with PTV-based optimization.

Worst-case scenario optimization resulted in target dose coverage and homogeneity (Table 2) similar to conventional optimization and decreased the dose to the OARs (Table 2). The worst-case scenario plans allowed lower $D_{1\%}$ doses in the spinal cord, lower mean doses (D_{mean}) in the total lungs, lower $D_{33\%}$ doses in the esophagus and heart, and lower V_{20} in the total lungs. For most end points, worst-case scenario optimization resulted in a better IMPT plan than conventionally optimized plans.

B. Plan robustness, target dose coverage, homogeneity, and normal tissue sparing when accounting for respiratory motion

Figure 3 depicts the transverse dose distributions for an axial CT slice for one of the nine patients with conventional optimization on the left and worst-case scenario optimization on

the right. Dose distributions with the patient at the end-expiration phase on the top and at the end-inspiration phase on the bottom are shown. Isodose lines in the conventionally optimized plan are perturbed by respiratory motion to a greater degree than in the worst-case scenario optimized plan for both phases.

The absolute differences of the $D_{95\%}$ and $D_{5\%}-D_{95\%}$ of the target dose at two respiratory phases (end-inspiration and end-expiration) are shown in Table 3 together with the nominal and worst-case dose to compare the plan robustness under the influence of respiratory motion. The impact of respiratory motion upon the plan robustness of normal tissues varies from organ to organ.

The worst of the corresponding DVH dose indices (ie, the smaller one for $D_{95\%}$ and the larger ones for other DVH dose indices) in the nominal dose at the two phases are shown in Table 4 to compare the target dose coverage, homogeneity and normal tissue sparing from both plans under the influence of respiratory motion. Again, worst-case scenario optimizations led to better plan robustness, better or comparable target dose coverage and homogeneity, and better or comparable OAR sparing with respiratory motion considered. However, respiratory motion degraded the target dose coverage and homogeneity and increased the doses to almost all OARs for both plans

We also used the robustness quantification statistical technique described in Sec. IIB to compare the plan quality and plan robustness in the end-inspiration and end-expiration phases under the influence of respiratory motion. The results shown in Figure 4 verified our previous conclusions.

IV. DISCUSSION

Our findings show that ITV-based worst-case scenario optimization with only patient setup and range uncertainties explicitly considered is superior to PTV-based conventional optimization in terms of plan robustness and plan quality, whether respiratory motion is considered or not. Our results confirm the findings of Stuschke *et al.*, (21), which did not account for respiratory motion and explore the influence of respiratory motion on the quality of plans generated using worst-case scenario optimization.

The isotropic expansion of 5 mm from ITV to PTV may not be adequate to account for range uncertainty. That is the reason why beam-specific PTVs (30) are used in PSPT and single field uniform dose (SFUD). However, these beam-specific PTVs are not applicable to the multi-field optimization (MFO) due to the highly heterogeneous dose distributions for each beam, both within and outside the target volume. Therefore a different “global” method, rather than a “local” margin solution, needs to be adopted in MFO-IMPT planning to mitigate the influence of uncertainties (31).

The worst-case scenario optimization method has important clinical implications for local tumor control. With photon radiation (60 Gy/30 fractions) and concurrent chemotherapy, the 5-year survival rate for patients with stage III non-small-cell lung cancer is only about 15%. Further improvements will likely require safe delivery of higher target doses without more side effects. Although proton therapy can potentially deliver higher doses to tumors while

keeping doses to normal tissues low, it is more sensitive to uncertainties. The improvement of ITV dose coverage in the perturbed dose distribution gives us more confidence in the doses delivered during treatment and may reduce the chance of local failure.

Patient set-up and range uncertainties are especially important in cases of lung cancer because of the substantial tissue heterogeneity within the treatment volume. The delivery of higher doses than desired to OARs may increase the risk of severe side effects. Therefore, it is critical for patient safety and quality of life that the delivered dose spares the OARs as much as possible even with uncertainties. Our results demonstrate that worst-case scenario optimization is superior or comparable to conventional PTV-based optimization at sparing OARs.

However, the clinical relevance of the differences between the two plans is questionable. We will calculate the corresponding tumor control probability (TCP) and normal tissue complication probability (NTCP) in a future study to ascertain whether the observed differences can lead to improved TCP and NTCP. Unfortunately for the time being we lack enough accurate data to perform meaningful calculations of TCP and NTCP for all tissues. Although the average difference appears to be small between the two planning techniques, the small differences might lead to large changes of TCP and NTCP due to the steep slopes of TCP and NTCP curves.

Respiratory motion blurs the dose to volumes surrounding the target, as indicated by reduced target dose coverage and homogeneity with worse OAR sparing (see the results presented in Section III.B). Although the worst-case scenario optimization method did not directly account for respiratory motion in the optimization algorithm, it was still superior to the conventional PTV-based method statistically. We speculate that the effects of respiratory motion are similar to set-up and range uncertainties and are partly mitigated by the worst-case scenario optimization. The impact of respiratory motion upon normal tissues is organ-dependent, which most likely is due to the relative position of normal tissue to the targets. In general, the plan robustness for normal tissues under the influence of respiratory motion is comparable between both plans. The worst-case scenario optimization does not necessarily lead to more robust dose distribution for normal tissues under the influence of respiratory motion. Additionally, the plan robustness, target dose coverage and homogeneity, and OAR sparing all deteriorate, when respiratory motion is accounted for, indicating that motion reduced the effectiveness of the optimization technique. Furthermore, the pattern of respiratory motion at the time of simulation may change during treatment,(32) which has been reported to degrade the quality of the resulting dose distribution in intensity-modulated photon therapy.(33) Optimizing proton therapy planning to account entirely for respiratory motion is beyond the scope of this paper and will be examined in our future analyses.

Finally, the interplay between dynamic delivery and tumor motion may lead to severely distorted dose distributions for a single fraction delivery.(3) As described in the Methods section, the patients included in this study were all selected with tumor motion less than 10 mm. In addition, the respiratory motion is less than or comparable to the spot spacing, which might reduce the influence of the interplay effect(12). Due to interplay effect some spots would be delivered in one phase while the remaining spots would be delivered in the other

phase (if only two phases are considered as in this work). Thus the dosimetric consequence such as DVH indices due to the interplay effect should lie between the ones calculated in those two phases separately (i.e., assuming all spots are delivered in either the end-inspiration or end-expiration phase). Therefore the way to evaluate of the impact of the respiratory motion has the interplay effect (at least for the end-inspiration and end-expiration phases) implicitly considered since we are taking the worse plan evaluation metrics between these two phases into account, although it is a conservative way. Our results show that the worst-case scenario optimization is superior to the PTV-based conventional optimization even with interplay effects implicitly considered. Although not optimal, the worst-case scenario optimization would be a better solution to mitigate the influence of residual respiratory motion, combined with set-up/range uncertainties in IMPT, to treat lung cancer with deep breath hold or beam gating. An appropriate repainting technique(9) might further minimize or eliminate the consequences of interplay effects. Therefore, this planning approach could have clinical impact, as several centers are treating, or are planning to treat, lung patients using breath hold or beam gating.

The current method has certain limitations. We have not studied the influence of spot size and spacing on the plan robustness. The degradation of plan quality due to the respiratory motions suggests that the plan quality may be improved if those issues are considered explicitly during the worst-case scenario optimization. The influence of the interplay effects are only taken into account implicitly in a very conservative fashion in the robustness evaluation. In the future, we plan to develop a 4D worst-case scenario optimization method for lung cancer IMPT planning that incorporates respiratory motion, respiratory motion variation, and interplay effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Comparison of RVHs derived from the worst-case scenario optimization plan (solid lines) and the PTV-based optimization plan (dashed lines). All curves were normalized to the total volume of the corresponding organs. RBE: relative biological effectiveness.

Figure 2.

Dose distributions in the axial plane illustrate that the worst-case scenario optimization plan was less sensitive to uncertainties than the conventional PTV-based optimization plan. Left panels: PTV-based plans. Right panels: worst-case scenario optimization plans. Top row: nominal position. Middle row: patient moved anteriorly by 5 mm. Bottom row: 3.5% range overshoot; patient moved anteriorly by 5 mm. ITV: orange segment; spinal cord: cyan. Solid blue arrows indicate the beam directions.

Figure 3.

Dose distributions in the axial plane illustrate that the worst-case scenario optimization plan was less sensitive to respiratory motion than the conventional PTV-based optimization plan. Left panels: PTV-based plans. Right panels: worst-case scenario optimization plans. Top row: at end-expiration phase. Bottom row: at end-inspiration phase. ITV: orange segment. Solid blue arrows indicate the beam directions.

(a) End-Inspiration

Figure 4.

Color wash represents the DVH bands for dose distributions covering all setup and proton range uncertainties for ITV and various organs for the worst-case scenario optimized plan (right column) and the conventionally optimized plan (left) for one typical case at (a) the end-inspiration phase and (b) the end-expiration phase. The solid lines are the DVHs for the nominal dose distribution (i.e., without consideration of uncertainties). The narrowness of CTV band for the robustly optimized plan indicates improved robustness.

Table 1

RVH AUCs, Averaged for 9 Patients

Target or tissue	Worst-case Scenario optimization AUC	Conventional optimization AUC	<i>P</i> value
Gross target volume	10.9	14.2	1.3e-3
Internal target volume	14.3	18.2	3.4e-4
Spinal cord	12.9	14.4	1.1e-3
Esophagus	25.9	26.6	0.038
Total lung	15.8	16.5	0.081
Heart	9.2	9.5	0.093
Contralateral lung	2.3	2.9	0.11
Ipsilateral lung	22.2	24.1	4.5e-4
Brachial plexus	14.1	15.2	0.25

RVH: root-mean-square dose volume histogram; AUC: area-under-RVH curve; PTV: planning target volume

Table 2

Target Dose Coverage, Homogeneity, and OAR Sparing, Averaged for 9 Patients

Tissue*	Worst-case Scenario optimization	Conventional optimization	P value
Gross target volume D ₉₅	99.3%	98.6%	0.010
Internal target volume D ₉₅	98.3%	97.9%	0.29
Gross target volume D ₅ – D ₉₅	3.11%	2.98%	0.26
Internal target volume D ₅ – D ₉₅	6.59%	5.76%	0.019
Spinal cord D _{1%} (Gy[RBE])	25.2	28.1	0.012
Total lung MLD (Gy[RBE])	16.0	16.2	0.11
Esophagus D _{33%} (Gy[RBE])	38.7	39.7	0.086
Esophagus D _{67%} (Gy[RBE])	4.2	4.5	0.091
Heart D _{33%} (Gy[RBE])	1.38	1.40	0.16
Brachial plexus D _{1%} (Gy[RBE])	22.2	24.1	0.25
Total lung V ₂₀	58.3%	59.6%	0.038

MLD, mean lung dose; OAR: organ-at-risk; PTV: planning target volume; RBE: relative biological equivalent.

* D₉₅ and D₅ are normalized by the prescribed dose; MLD, D_{1%}, D_{33%}, and D_{67%} are given in Gy (RBE); V₂₀ is normalized by the total lung volume.

Table 3

Absolute differences of $D_{95\%}$ and $D_{5\%}-D_{95\%}$ in both the worst-case and nominal dose distribution at the two phases, Averaged for 9 Patients, Accounting for the Effect of Organ Motion. The minimum and maximum among those 9 patients are shown in the bracket.

Target or tissue	Worst-case scenario optimization	Conventional optimization	<i>P</i> value
GTV D_{95} (worst-case)	1.29% (0.025%,3.8%)	1.72% (0.20%,4.6%)	0.028
ITV D_{95} (worst-case)	2.97% (0.45%,10%)	3.83% (0.31%,9.6%)	0.21
GTV $D_5 - D_{95}$ (worst-case)	1.00% (0.0064%,2.5%)	1.54% (0.073%,3.4%)	0.027
ITV $D_5 - D_{95}$ (worst-case)	4.92% (0.048%,10.8%)	4.89% (0.15%,8.8%)	0.35
GTV D_{95} (nominal)	0.29% (0.016%,0.57%)	0.67% (0.073%,1.4%)	0.029
ITV D_{95} (nominal)	0.64% (0.0096%,2.7%)	1.32% (0.35%,3.5%)	0.0039
GTV $D_5 - D_{95}$ (nominal)	0.37% (0.0087%,0.98%)	0.81% (0.20%,2.3%)	0.074
ITV $D_5 - D_{95}$ (nominal)	0.70% (0.10%,3.0%)	1.08% (0.042%,2.7%)	0.13

GTV: Gross target volume; ITV: Internal target volume

Table 4

Target Dose Coverage, Homogeneity, and OAR Sparing, Accounting for the Effect of Organ Motion, Averaged for 9 Patients. The minimum and maximum among those 9 patients are shown in the bracket.

Tissue [*]	Worst-case scenario optimization	Conventional optimization	P value
Gross target volume D ₉₅	99.0% (98.1%,99.6%)	97.5% (95.1%,99.0%)	2.6e-3
Internal target volume D ₉₅	97.3% (93.3%,99.2%)	95.9% (90.9%,98.6%)	9.8e-3
Gross target volume D ₅ – D ₉₅	5.5% (0.8%,15.3%)	8.4% (1.5%,27.4%)	0.020
Internal target volume D ₅ – D ₉₅	10.4% (2.4%,22.9%)	13.2% (2.7%,32.7%)	0.055
Spinal cord D _{1%} (Gy[RBE])	31.8 (9.2,55.9)	36.5 (9.5,62.0)	0.035
Total lung MLD (Gy[RBE])	17.2 (13.6,21.6)	17.3 (13.9,21.0)	0.36
Esophagus D _{33%} (Gy[RBE])	40.9 (6.5,65.6)	42.5 (6.8,68.9)	0.0014
Esophagus D _{67%} (Gy[RBE])	4.34 (0,17.0)	4.69 (0,18.7)	0.016
Heart D _{33%} (Gy[RBE])	1.58 (0,5.3)	1.63 (0,5.3)	0.11
Brachial plexus D _{1%} (Gy[RBE])	24.85 (0.18,64.4)	24.88 (0.21,67.7)	0.44
Total lung V ₂₀	62.7% (46.3%,78.2%)	63.5% (47.1%,78.8%)	0.051

MLD, mean lung dose; OAR: organ-at-risk; PTV: planning target volume; RBE: relative biological equivalent..

* D₉₅ and D₅ are normalized by the prescribed dose; MLD, D_{1%}, D_{33%}, and D_{67%} are given in Gy (RBE); V₂₀ is normalized by the total lung volume. The DVH dose indices shown here are the worse of the corresponding DVH dose indices (ie, the smaller one for D_{95%} and the larger ones for other DVH dose indices) at these two phases.