Comparison between 4D Robust Optimization Methods for Carbon-Ion Treatment Planning

Authors: Li, Qiang, Wang, Wenyu, Ma, Yuanyuan, Zhang, Hui, Zhang, Xinyang, Yang, Jingfen, Liu, Xinguo, Li, Qiang

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Abstract

Intensity-modulated particle therapy (IMPT) with carbon ions is comparatively susceptible to various uncertainties caused by breathing motion, including range, setup, and target positioning uncertainties. To determine relative biological effectiveness-weighted dose (RWD) distributions that are resilient to these uncertainties, the reference phase-based four-dimensional (4D) robust optimization (RP-4DRO) and each phase-based 4D robust optimization (EP-4DRO) method in carbon-ion IMPT treatment planning were evaluated and compared. Based on RWD distributions, 4DRO methods were compared with 4D conventional optimization using planning target volume (PTV) margins (PTV-based optimization) to assess the effectiveness of the robust optimization methods. Carbon-ion IMPT treatment planning was conducted in a cohort of five lung cancer patients. The results indicated that the EP-4DRO method provided better robustness (P=0.080) and improved plan quality (P=0.225) for the clinical target volume (CTV) in the individual respiratory phase when compared with the PTV-based optimization. Compared with the PTV-based optimization, the RP-4DRO method ensured the robustness (P = 0.022) of the dose distributions in the reference breathing phase, albeit with a slight sacrifice of the target coverage (P=0.450). Both 4DRO methods successfully maintained the doses delivered to the organs at risk (OARs) below tolerable levels, which were lower than the doses in the PTV-based optimization (P<0.05). Furthermore, the RP-4DRO method exhibited significantly superior performance when compared with the EP-4DRO method in enhancing overall OAR sparing in either the individual respiratory phase or reference respiratory phase (P<0.05). In general, both 4DRO methods outperformed the PTV-based optimization in terms of OAR sparing and robustness.

Full Text

Preamble

Comparison of 4D Robust Optimization Methods for Carbon-Ion Treatment Planning

Wenyu Wang,[1,2,3,4] Yuanyuan Ma,[1,2,3,4] Hui Zhang,[1,2,3,4] Xinyang Zhang,[1,2,3,4] Jingfen Yang,[1,2,3,4] Xinguo Liu,[1,2,3,4] and Qiang Li[1,2,3,4,5]

[1]Institute of Modern Physics, Chinese Academy of Sciences, Lanzhou 73000, China
[2]Key Laboratory of Heavy Ion Radiation Biology and Medicine of Chinese Academy of Science, Lanzhou 730000, China
[3]Key Laboratory of Basic Research on Heavy Ion Radiation Application in Medicine, Gansu Province, Lanzhou 730000, China
[4]University of Chinese Academy of Sciences, Beijing 100049, China
[5]Putian Lanhai Nuclear Medicine Research Center, Putian 351152, China

Intensity-modulated particle therapy (IMPT) with carbon ions is particularly susceptible to various uncertainties caused by breathing motion, including range, setup, and target positioning uncertainties. To determine relative biological effectiveness-weighted dose (RWD) distributions that are resilient to these uncertainties, we evaluated and compared two four-dimensional robust optimization (4DRO) methods in carbon-ion IMPT treatment planning: reference phase-based 4D robust optimization (RP-4DRO) and each phase-based 4D robust optimization (EP-4DRO).

Based on RWD distributions, we compared these 4DRO methods with conventional 4D optimization using planning target volume (PTV) margins (PTV-based optimization) to assess the effectiveness of robust optimization approaches. Carbon-ion IMPT treatment planning was performed for a cohort of five lung cancer patients. The results indicated that the EP-4DRO method provided better robustness ($P = 0.080$) and improved plan quality ($P = 0.225$) for the clinical target volume (CTV) in individual respiratory phases compared with PTV-based optimization. Relative to PTV-based optimization, the RP-4DRO method ensured robustness ($P = 0.022$) of dose distributions in the reference breathing phase, albeit with a slight sacrifice in target coverage ($P = 0.450$). Both 4DRO methods successfully maintained doses to organs at risk (OARs) below tolerable levels, which were lower than those achieved with PTV-based optimization ($P < 0.05$). Furthermore, the RP-4DRO method exhibited significantly superior performance compared with the EP-4DRO method in enhancing overall OAR sparing in both individual and reference respiratory phases ($P < 0.05$). In general, both 4DRO methods outperformed PTV-based optimization in terms of OAR sparing and robustness.

Keywords: Intensity-modulated particle therapy, Carbon-ion radiotherapy, Uncertainties, Four-dimensional optimization, Lung cancer, Relative biological effectiveness-weighted dose, Robustness, Treatment planning system

Introduction

Intensity-modulated particle therapy (IMPT) with carbon ions can deliver higher doses to the target volume while significantly sparing adjacent organs at risk (OARs) [**?**, **?**]. However, the sharp dose falloff behind the pristine Bragg peak of carbon-ion beams makes dose distributions highly sensitive to uncertainties, which greatly diminishes the effectiveness of IMPT [**?**]. Three of the most pertinent uncertainties in carbon-ion dose distributions include: (1) range uncertainty introduced by uncertainty in computed tomography (CT) numbers and their conversion to relative stopping power [**?**]; (2) setup uncertainty related to lack of reproducibility in patient positioning [**?**]; and (3) uncertainties introduced by respiratory motion, especially for patients with lung cancers [**?**]. Comparing PTV-based optimization with robust optimization represents a widely used approach for evaluating treatment plan robustness. Although the PTV concept has been employed in some studies of carbon-ion radiotherapy [**?**], it is insufficient for this modality because dose distributions are influenced by various factors not only at target edges but also within the target volume itself [**?**].

To mitigate the impact of these uncertainties in carbon-ion IMPT, various three-dimensional robust optimization (3DRO) methods have been developed, including probabilistic optimization [**?**, **?**], voxel-wise worst-case robust optimization [**?**], and worst-case scenario robust optimization [**?**]. These methods aim to incorporate uncertainties directly into the optimization process. Probabilistic methods optimize treatment plans based on numerous dose distributions produced by randomly sampling setup and range uncertainty scenarios according to assumed probability distributions [**?**]. Voxel-wise worst-case robust optimization considers the minimum and maximum doses from all uncertainty scenarios for each voxel within the target volume and maximum doses for each voxel within normal tissues, optimizing a single objective function based on these worst-case dose distributions during iterations. The worst-case scenario robust optimization method evaluates the objective function for all uncertainty scenarios and selects the worst objective function score during the iteration process. Recent studies have shown that 3DRO methods can minimize dose distribution variance under different uncertainty scenarios and improve treatment planning robustness [**?**].

Target motion and motion-induced range changes play important roles in particle radiotherapy. However, the effectiveness of 3DRO methods in mitigating respiratory motion effects on lung cancer therapy is limited [**?**]. To explicitly account for respiratory motion in IMPT, different strategies have been proposed, primarily including respiratory gating and breath-holding. Unfortunately, these methods have limitations regarding treatment time and patient tolerance requirements. Additionally, online motion tracking [**?**] is indispensable for moving targets during treatment to reduce breathing motion impact, but this remains technically challenging. Another approach proposed by Graeff et al. [**?**] suggested that 4D optimization based on all motion states is valid for carbon-ion

therapy. Liu et al. [**?**] introduced a reference phase-based 4D robust optimization (RP-4DRO) method that optimizes cumulative 4D dose distributions. Ge et al. [**?**] proposed a method termed each phase-based 4D robust optimization (EP-4DRO), which optimizes dose distributions based on individual respiratory phases. Wolf et al. [**?**] proposed a robust nonlinear RBE-weighted optimization method to expand carbon-ion IMPT, exploring potential improvements in plan robustness and critical organ sparing. These studies confirm that 4DRO methods can improve plan robustness and offer better control over uncertainties during treatment. However, a persistent lack of comparative analyses among different 4DRO methods in carbon-ion IMPT treatment planning has hindered comprehensive understanding of each method's distinct characteristics.

Relative biological effectiveness (RBE), defined as the ratio of photon dose to ion dose producing the same biological effect under identical conditions [**?**], is widely used in particle therapy. A constant RBE value of 1.1 is clinically accepted for protons. However, carbon-ion RBE values must be described by mathematical models rather than a single parameter due to their complex dependence on physical and biological factors. Consequently, carbon-ion treatment planning requires RBE-weighted doses (RWD), defined as the product of physically absorbed dose and RBE. Several models have been proposed, including the mixed beam model, the local effect model (LEM), and the microdosimetric kinetics model (MKM) [**?**], facilitating carbon-ion treatment planning using RWD.

An appropriate robust optimization method is crucial for addressing dose perturbations arising from various uncertainties. To our knowledge, no previous studies have compared RP-4DRO and EP-4DRO methods. While it is acknowledged that the RP-4DRO method does not explicitly optimize dose distributions in individual breathing phases, evaluating dose distributions in individual phases remains necessary for clinical implementation. To assess the effectiveness of 4DRO methods in carbon-ion IMPT, a comparative investigation is indispensable. The innovation of this study lies in comparing and evaluating two theoretically different robust optimization methods in terms of RWD distributions in carbon-ion IMPT treatment planning.

Materials and Methods

A. Treatment Planning

MatRad [**?**], an open-source treatment planning system (TPS) developed for educational and research purposes, supports carbon-ion IMPT treatment planning. The available carbon-ion energies in MatRad range from 115.23 MeV/u to 398.84 MeV/u, corresponding to penetration depths of 32.68 mm to 294.25 mm in water. Alpha-beta ratios of 10 and 2 were selected for target volume and normal tissue, respectively. The dose grid was set to 3 mm $\times$ 3 mm $\times$ 3 mm. The pencil beam scanning (PBS) method with spot scanning was employed, enabling conformal dose distributions for irregularly shaped tumors and improving beam utilization [**?**]. Gaussian-shaped carbon-ion beam spot sizes

range from 11.80 mm to 8.01 mm (full width at half maximum, FWHM) for energies between 115.23 MeV/u and 398.84 MeV/u. A spot spacing of 3 mm was used in both lateral and longitudinal directions.

Carbon-ion IMPT treatment planning was performed for five patients with lung tumor lesions. For each patient, 4DCTs were acquired with 10 motion states. To reduce computational memory consumption, both 4DRO methods were developed using three significantly different breathing phases: 0% expiration phase, 80% expiration phase, and 40% inspiration phase. The 0% expiration phase was defined as the reference breathing phase.

For PTV-based optimization, the PTV was generated by extending the union of CTVs across all three phases with a 5-mm safety margin. This margin magnitude was derived from conventional photon treatment planning [**?**]. Dose distributions were calculated for the three respiration phases without accounting for setup and range uncertainties. Both 4DRO methods were performed on the CTV for each phase without incorporating any margins. Setup uncertainties were assumed as $±$5 mm in the ±x, ±y, and ±z directions. Range uncertainty parameters were set to $±$3.5% when computing water-equivalent depth. Each breathing phase had eight uncertain dose scenarios and one nominal dose scenario.

Tumor size, location, motion magnitude, and beam angles for the five patients are listed in Table 1 . The CTV centroids in the right–left (RL), anterior–posterior (AP), and superior–inferior (SI) directions were recorded for the three breathing phases, with maximum centroid displacement used to determine motion magnitude. Patient datasets included 4DCT images with CTV and OARs delineated by an experienced physician following guidelines provided in [**?**]. The prescription for all patients was 60 Gy(RBE)/15 fractions, with threshold doses of 45, 20, and 30 Gy(RBE) for the spinal cord, lungs, and heart, respectively. The LEM was used to calculate RBE values.

TABLE 1. Tumor locations, volumes, and motion magnitudes of the patients under investigation.

Patient ID	Tumor location	Tumor volume	Motion angle
1	Right hilar	[data]	220 / 140
2	Right hilar	[data]	220 / 140
3	Left hilar	[data]	210 / 140
4	Right lower	[data]	330 / 45
5	Right lower	[data]	330 / 45

B. 4D Robust Optimization

Liu et al. [**?**] proposed a robust version of the 4D optimization method and demonstrated that this approach can enhance the robustness of cumulative 4D

dose distribution. The physical absorbed dose distributions (d_{sik,jw_j}) in different setup and range uncertainty scenarios were calculated for the breathing phases of 4DCT datasets, where w_j represents the intensity weight of beamlet j, and d_s represents the influence matrix describing the distribution of beamlet j in breathing phase k to voxel i_k in uncertainty scenarios. We define s as each uncertainty scenario considered during treatment planning optimization and S as the set of all scenarios. During optimization, a non-negative vector w_j^2 is used to transform the constrained optimization problem ($w \geq 0$) into an unconstrained problem. The cumulative physically absorbed dose distributions were deformed to the reference breathing phase using the registration algorithm in MatRad. The cumulative RWD distributions D_s^i were computed using these cumulative physically absorbed dose distributions. Specifically, D_s^i were employed in a standard quadratic objective function to design carbon-ion treatment plans. The worst-case scenario robust optimization was conducted as follows:

$$\min f(w) = \sum_{N\in\text{Target}} \left\{ q_{n,\max} \max_{s\in S} (D_s^i - D_{\text{pre}})^2 + q_{n,\min} \min_{s\in S} (D_s^i - D_{\text{pre}})^2 \right\} + \sum_{M\in\text{OAR}} q_{m,\max} \max_{s\in S} H(D_s^i - D_o)(D_s^i -$$

where D_{pre} and D_o denote the prescription dose in the target volume and dose constraints on relevant tissues, respectively. Furthermore, N and M denote the numbers of target volumes and OARs, respectively. Parameters $q_{n,\max}$, $q_{n,\min}$, and $q_{m,\max}$ are penalty factors for target volumes and OARs, with values of $q_{n,\max} = 1.0$, $q_{n,\min} = 1.0$, and $q_{m,\max} = 1.0$ used in this study. The step function H is mathematically defined as $H = 1.0$ when $D_s^i > D_o$ and $H = 0.0$ otherwise. The ultimate optimization objective is to minimize the objective function $f(w)$ to achieve optimal dose distributions over relevant voxels.

The RP-4DRO method did not explicitly address optimization of dose distributions in individual breathing phases, leaving unclear whether robustness in individual respiratory phases could be ensured. Ge et al. [**?**] proposed the EP-4DRO method to address uncertainty in proton treatment planning. RWD distributions D_s^{ik} in different setup and range uncertainty scenarios were calculated for all breathing phases of 4DCT. The worst dose distributions for each breathing phase were determined by selecting the worst objective score, after which the worst dose distributions for all phases were simultaneously optimized. The objective function is expressed as:

$$\min f(w) = \sum \left\{ \sum_{N\in\text{Target}} q_{n,\max} \max_{s\in S} (D_s - D_{\text{pre}})^2 + q_{n,\min} \min_{s\in S} (D_s - D_{\text{pre}})^2 \right\} + \sum \sum \sum_{M\in\text{OAR}} q_{m,\max} \max_{s\in S} H(I$$

All parameter settings were identical to those in the RP-4DRO method. During optimization iteration, objective function values were calculated for each dose scenario and the worst scenario was selected.

C. Plan Evaluation

To maintain consistency, resulting dose distributions for volumes of interest (VOIs) were evaluated and compared using identical parameters. Nine dose distributions for each breathing phase (six setup uncertainty scenarios, two range uncertainty scenarios, and one nominal scenario) were calculated. Dose-volume histogram (DVH) bands derived from the 27 dose distributions (nine scenarios for three breathing phases) were analyzed to compare treatment plan robustness. For PTV-based optimization, dose distributions were recalculated for each breathing phase using the optimized spot intensities for each of the nine uncertainty scenarios. A narrower DVH band indicates greater robustness, implying relatively minimal dose distribution changes under uncertainty influence. Evaluating DVHs with nine accumulated dose distributions is essential [**?**]; thus, DVHs derived from these nine accumulated dose distributions were also analyzed, with dose accumulation assessed across the three breathing phases.

Dose distribution conformity index (CI) and target heterogeneity index (HI) were computed using the following equations:

$$\mathrm{CI} = \frac{\mathrm{TV}_{95\%}}{V_{95\%}} \quad \text{and} \quad \mathrm{HI} = \frac{D_{5\%} - D_{95\%}}{D_{\mathrm{pre}}}$$

Specifically, $\mathrm{TV}_{95\%}$ denotes the target volume receiving 95% of the prescription dose, while $V_{95\%}$ represents the total volume receiving at least 95% of the prescribed dose; CTV is the target volume for all three methods. CI measures how well target dose distributions conform to the target volume, with values closer to 1.0 indicating greater conformity. HI reflects target dose distribution homogeneity, with values closer to 0.0 indicating greater homogeneity. To compare target coverage, the index $D_{95\%}$ represents the dose received by 95% of the target volume, with values closer to the prescribed dose indicating better target coverage.

Normal tissue sparing was evaluated by comparing different treatment plans optimized using different methods. Evaluation indices including lung D_{mean}, lung V_{20}, lung V_5, heart D_{mean}, heart V_{30}, and spinal cord D_{max} were analyzed and compared. Given that dose distributions exhibited non-Gaussian profiles, statistical analysis was conducted using the Wilcoxon signed-rank test [**?**] to compare PTV-based optimization and 4DRO methods, with $P < 0.05$ considered statistically significant.

Results

Five lung cancer patients were evaluated for potential differences. All methods focused on RWD. This section presents key findings for these patients.

A. Exemplary Patient

Fig. 1 [Figure 1: see original paper] shows DVH bands for CTV and OARs derived from the 27 dose distributions for Patient 1 as an example. Results for PTV-based optimization, RP-4DRO, and EP-4DRO methods are shown in Figs. 1a, 1b, and 1c, respectively. Dose distributions without considering uncertainties for the reference phase (nominal scenario) are highlighted by black solid lines. For Patient 1, bandwidths at $D_{95\%}$ for PTV-based optimization, RP-4DRO, and EP-4DRO methods were 8.92, 8.77, and 5.29 Gy(RBE), respectively. Correspondingly, bandwidths at $D_{5\%}$ were 2.11, 2.11, and 1.68 Gy(RBE). The planning objective for CTV coverage was set to $D_{95\%}/D_{\text{pre}} \geq 95\%$ in the nominal scenario. CTV coverages in the nominal scenario for PTV-based optimization, RP-4DRO, and EP-4DRO methods were 94.86%, 93.51%, and 96.73%, respectively.

For DVHs of normal structures, both 4DRO methods achieved narrower bands compared to PTV-based optimization for lung, heart, and spinal cord sparing. Nominal views of accumulated 4D dose distributions in the reference phase for Patient 1 are presented in Figs. 1d, 1e, and 1f. Dose at CTV edges was reduced for both 4DRO methods compared to PTV-based optimization. Notably, the RP-4DRO method (Fig. 1e) showed hot spots in the medial area of CTV compared with the EP-4DRO method (Fig. 1f).

B. Entire Patient Cohort

Fig. 2 [Figure 2: see original paper] shows target coverage indices for the nominal scenario. Compared with PTV-based optimization, target coverage indices achieved by the RP-4DRO method were relatively low, except for Patient 3 ($P = 0.383$). These indices were also below the constraint ($D_{95\%}/D_{\text{pre}} \geq 95\%$). Conversely, the EP-4DRO method exhibited superior performance in target coverage for all patients ($P = 0.225$).

Fig. 3 [Figure 3: see original paper] shows robustness evaluation results and plan qualities for the three optimization methods across five patients. Bandwidths at 95% and 5% CTV volumes for all three methods are shown in Figs. 3a and 3b, respectively, with lower values indicating higher robustness. Based on experimental findings, dose distributions within CTV derived from EP-4DRO exhibited narrower bandwidths than those achieved through PTV-based optimization, except for Patient 3. Similarly, the RP-4DRO method yielded narrower bandwidths compared to PTV-based optimization, with the exception of Patients 2 and 4.

Figs. 3c and 3d present HI and CI values for all 27 scenarios across five patients, with error bars indicating one standard deviation. For the EP-4DRO method, HI values were generally lower than those for RP-4DRO and PTV-based optimization ($P = 0.345$), except for Patient 4, indicating better dose homogeneity at target boundaries. Conversely, the RP-4DRO method yielded relatively higher HI values, indicating worse dose homogeneity in individual res-

piration phases ($P = 0.107$). As shown in Fig. 3d, CI values obtained using EP-4DRO were higher compared to PTV-based optimization ($P = 0.160$) and RP-4DRO method, with EP-4DRO producing higher CI values than PTV-based optimization for all patients except Patient 4 ($P = 0.005$).

As shown in Fig. 4 [Figure 4: see original paper], dose-volume indices for OARs were also calculated. Comparative analysis revealed that the RP-4DRO method delivered lower doses to the lung ((left/right) lung D_{mean}, $P < 0.05$; left lung V_{20}, $P = 0.068$; (left/right) lung V_5, $P < 0.05$; and right lung V_{20}, $P < 0.05$). As shown in Fig. 5 [Figure 5: see original paper], both 4DRO methods yielded lower indices for heart and spinal cord compared to PTV-based optimization ($P < 0.05$), indicating these organs received lower doses. Notably, for all five patients, the RP-4DRO method consistently exhibited the lowest doses to lungs and heart across individual breathing phases. However, RP-4DRO did not demonstrate superiority in maintaining lower spinal cord doses compared with EP-4DRO. P-values indicate that differences in OAR indices between the two 4DRO methods were statistically significant.

The aforementioned results illustrate 27 dose distributions for three respiratory phases. However, for clinical implementation, it is necessary to compare accumulated dose distributions across the three respiratory phases. Bandwidth at 95% CTV volume and target coverage of cumulative distributions are shown in Fig. 6 [Figure 6: see original paper]. The RP-4DRO method showed smaller bandwidth at 95% CTV volume compared to PTV-based optimization ($P = 0.022$). Conversely, EP-4DRO did not guarantee small bandwidths for Patients 2 and 5 compared with PTV-based optimization ($P = 0.272$). Target coverages generated by RP-4DRO ($P = 0.45$) and EP-4DRO ($P = 0.066$) were lower than that of PTV-based optimization. Dose distributions in OARs are illustrated in Fig. 7 [Figure 7: see original paper]. Compared with PTV-based optimization, both 4DRO methods achieved lower doses in lung, heart, and spinal cord ($P < 0.05$). Notably, EP-4DRO resulted in the lowest doses in lungs and heart. In contrast, EP-4DRO was not superior in maintaining the lowest cumulative dose distribution to the spinal cord, implying that accumulated dose distributions generated by both 4DRO methods are more conservative.

Discussion

Both 4DRO methods have been proposed to improve treatment plan robustness for carbon-ion IMPT. Although many studies have investigated patient responses to various optimization methods across diverse cancers, no direct comparisons between RP-4DRO and EP-4DRO methods have been conducted. Consequently, this study systematically compared and evaluated both 4DRO methods in carbon-ion IMPT treatment planning.

The EP-4DRO method can ensure plan robustness in individual respiratory phases, as shown in Figs. 3a and 3b. Conversely, the RP-4DRO method ensures robustness of cumulative dose distributions, specifically in the reference

respiratory phase, as illustrated in Fig. 6a, because it does not explicitly optimize dose distributions in individual breathing phases.

Regarding target heterogeneity (Figs. 3c and 3d), EP-4DRO shows superior dose homogeneity inside target boundaries compared to PTV-based optimization and RP-4DRO. Both 4DRO methods outperformed PTV-based optimization in dose distribution conformity, except for Patient 4. This discrepancy can be attributed to the inherent challenge of ensuring dose-distribution conformity for smaller target movements during optimization.

Guaranteeing target coverage is vital for carbon-ion IMPT treatment planning. Regarding target coverage indices in individual respiratory phases, EP-4DRO ensured adequate coverage, whereas RP-4DRO sacrificed target coverage, except for Patient 3. As shown in Fig. 6b, both 4DRO methods sacrificed target coverage in the reference respiratory phase. Notably, target coverage remained unsatisfactory for uncertainty scenarios, as shown in Fig. 1. Furthermore, target coverage achieved by EP-4DRO in individual respiratory phases differed from that observed in the reference phase, potentially due to deformable image registration accuracy.

Both 4DRO methods demonstrate superior OAR sparing compared with PTV-based optimization, as indicated in Figs. 4, 5, and 7. An important finding demonstrated that RP-4DRO exhibited superior performance to EP-4DRO in protecting lungs and heart in both individual and reference respiratory phases. However, RP-4DRO showed no advantage over EP-4DRO in spinal cord sparing. P-values indicate that differences in OAR indices between the two methods were statistically significant.

Generally, both 4DRO methods yielded different results due to different dose distributions selected during optimization. Ge et al. [**?**] demonstrated that EP-4DRO maintained robustness even if patients did not breathe consistently fraction-by-fraction over the treatment course. Our study suggests that carbon-ion IMPT treatment planning using EP-4DRO is superior to RP-4DRO in terms of robustness and plan quality while being flexible. The RP-4DRO method exhibited superior OAR protection. Thus, if OAR sparing is the priority, RP-4DRO should be used. Conversely, if robustness is the priority, EP-4DRO should be chosen. Furthermore, results highlight that carbon-ion IMPT treatment planning with both 4DRO methods leads to worse target coverage for small target volumes, as observed in Patient 4. Therefore, caution should be exercised when utilizing both 4DRO methods for small-volume tumors. Compared to proton treatment planning, the main distinction in 4D robust optimization is optimization of RBE-weighted dose distributions with variable RBE values. This study further investigated application of 4D robust optimization methods to carbon-ion treatment planning.

It is crucial to recognize inherent limitations of this study. These five lung cancer patients may not comprehensively represent all lung cancer cases. Future investigations must carefully consider larger patient cohorts to ensure more inclusive

analysis. Moreover, this study only included three breathing phases; subsequent steps should adopt additional respiratory phases to ascertain whether similar results can be obtained. Finally, it is essential to explore potential uncertainties associated with RBE in future research, as RBE values play a critical role in calculating carbon-ion biological dose.

The interplay effect due to interference between dynamic beam delivery and target motion leads to dose distribution deterioration. Severity of interplay effects could potentially be reduced through favorable selection of treatment parameters such as beam direction, scan speed, and scan path. However, these strategies do not fully eliminate relevant interplay effects. Bert et al. [**?**] expected relevant residual interplay effects even after 30 fractions. Richter et al. [**?**] suggested that increasing beam spot size represents an efficient motion mitigation option readily available at most scanning facilities, especially for large tumors. Reduced internal dose gradients decrease susceptibility to interplay effects in robust dose distributions [**?**]. For fair comparison with perfectly synchronized 4D robust optimization, interplay effects were not considered in this study. Nevertheless, efforts to further reduce interplay effects should be differentially considered for particle therapies using different ion species.

Conclusions

In this study, both 4DRO approaches were implemented for carbon-ion IMPT treatment planning, explicitly incorporating range, setup uncertainty, and target positioning uncertainties due to breathing motion. The clinical application potential of both 4DRO methods was evaluated in five lung cancer patients. Our results indicated that EP-4DRO exhibits superior robustness and plan quality, whereas RP-4DRO performs better in OAR sparing. Both 4DRO methods outperformed PTV-based optimization when confronted with various uncertainties encountered during carbon-ion IMPT treatment planning.

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Note: Figure translations are in progress. See original paper for figures.