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Carbon-Ion Spatially Fractionated Radiotherapy: 3D Lattice-Vertex Optimization to Amplify High-LET Dose Peaks and Biological Efficacy

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ABSTRACT

We performed a systematic plan comparison between carbon-ion and photon lattices created on identical tumor geometries and proposed a novel 3D lattice-vertex optimization strategy that actively steers high-linear energy transfer (LET) spots into pre-defined peak regions, maximizing biological gain without compromising normal-tissue sparing. When utilizing the same lattice vertex arrangements, carbon-ion treatment plans demonstrated superior protection for organs at risk (OARs) and yielded substantially greater peak-to-valley dose ratios (PVDRs) compared to photon-based approaches. Furthermore, the application of the newly introduced sphere-placement optimization algorithm resulted in a marked elevation of both the minimum and average dose-averaged LET (LETd) within the lattice spheres. Notably, this algorithmic enhancement did not produce any statistically significant variations in the PVDR or OARs doses when benchmarked against standard carbon-ion lattice techniques.

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INTRODUCTION

Spatially Fractionated Radiotherapy (SFRT), particularly Lattice Radiation Therapy (LRT), creates alternating high-dose peaks and low-dose valleys within tumors[1]. This spatial modulation leverages radiobiological mechanisms like the bystander effect to deliver ultra-high local doses while sparing normal tissues, offering new solutions for large, radioresistant, or adjacent-to-critical-structure tumors. Early studies show LRT improves local control while reducing toxicity compared to conventional uniform irradiation. While photons are currently standard, carbon ions offer unique advantages. Their sharp Bragg peaks and minimal lateral scattering provide superior dose conformity. Crucially, their high LET near the Bragg peak yields a higher Relative Biological Effectiveness (RBE), enhancing lethality against radioresistant cells[2,3] . However, systematic comparisons between photon and carbon ion LRT remain scarce.
In LRT planning, high-dose peak positioning guides dose optimization. Unlike photons, carbon ion efficacy heavily depends on LET. High LET correlates with greater DNA double-strand breaks and improved tumor control[4,5]. Therefore, precisely aligning high-LET regions with dose peaks could yield significant biological gains, especially against radio resistance.
This study systematically compares carbon ion and photon LRT plans using identical target and lattice geometries, quantifying differences in physical dose distribution, target coverage, organ-at-risk sparing, and dose fall-off. Furthermore, by optimizing the 3D layout of lattice vertices, we aim to actively guide high-LET regions to precisely cover predefined high-dose peaks or radioresistant sub-regions. This approach seeks to maximize the biological efficacy of carbon ion LRT while maintaining or improving normal tissue protection, providing a theoretical basis for its clinical application.

METHODS AND MATERIALS

Lattice Vertex Arrangement Optimization
Our previous phantom studies have demonstrated that reducing the mean width of SOBP width can effectively enhance the LETd distribution within spherical targets. To achieve this physical advantage, we developed a lattice orientation optimization method that minimizes the mean SOBP width by adjusting the global rotational state of the lattice. The optimization problem was solved using a genetic algorithm.

Plan comparison
Twelve patients previously treated with photon SFRT were re-planned: a 20 Gy single-fraction lattice prescription was assigned to the gross tumor volume (GTV). Three plans were generated for each case: photon lattice, standard carbon-ion lattice, and carbon-ion lattice with vertex-optimized spot placement. Plan quality metrics included peak-to-valley dose ratios (PVDR1) (D10/D90 of GTV) and PVDR2 (mean lattice dose / mean non-lattice GTV dose), OAR doses, and LET indicators within lattice peaks: minimum LETd and volumes receiving LETd > 40, 60, 80 and 100 keV·µm^{-1}. Two-tailed paired t-tests were used for statistical comparison.

RESULTS

Under identical lattice vertex configurations, carbon-ion plans exhibited significantly higher peak-to-valley dose ratios than photon plans (PVDR1: 232.31 ± 321.62 vs. 10.62 ± 13.10; PVDR2: 5.71 ± 5.96 vs. 2.51 ± 1.60; both $p < 0.05$). Maximum doses to the esophagus, heart, skin, and spinal cord were consistently lower with carbon ions (esophagus: 25.45 ± 44.62 cGy vs. 587 ± 296.51 cGy; heart: 249.09 ± 263.61 cGy vs. 614.73 ± 586.2 cGy; skin: 784.82 ± 221.86 cGy vs. 1176.45 ± 552.64 cGy; spinal cord: 17.64 ± 25.61 cGy vs. 510.82 ± 303.9 cGy; all $p < 0.05$). After implementing the proposed vertex-optimized sphere-placement algorithm, no statistically significant differences were observed in PVDR1, PVDR2, or maximum doses to the aforementioned organs-at-risk relative to the conventional carbon-ion lattice (all $p > 0.05$). However, both the minimum and mean dose-averaged LET (LETd) within the lattice spheres increased significantly (minimum LETd: 52.04 ± 10.33 keV µm^{-1} vs. 44.45 ± 10.95 keV µm^{-1}; mean LETd: 79.17 ± 6.6 keV µm^{-1} vs. 75.41 ± 7.24 keV µm^{-1}; both $p < 0.05$).

Table 1. Dosimetric comparison among photon SFRT plan (plan X), carbon ion SFRT plan (plan C), and carbon ion SFRT plan based on optimized vertices arrangement (plan C'). .

	plan X	plan C	plan C'
$PVDR_1$	10.62±13.10	232.31±321.62	267.41±495.95
$PVDR_2$	2.51±1.60	5.71±5.96	3.49±0.95
body-GTV V_{6Gy} (cc)	457.75±382.71	37.08±48.58	37.98±31.77
body-GTV V_{3Gy} (cc)	1478.43±949.68	161.2±123.07	187.73±103.36
Vertices minimize LET_d (kev/µm)	-	44.45±10.95	52.04±10.33
Vertices mean LET_d (kev/µm)	-	75.41±7.24	79.17±6.6
$V_{40\ keV/\mu m}$ in vertices (cc)	-	10.45±8.90	16.12±11.54
$V_{60\ keV/\mu m}$ in vertices (cc)	-	8.04±6.89	10.14±5.94
$V_{80\ keV/\mu m}$ in vertices (cc)	-	4.37±5.32	4.38±2.41
$V_{100\ keV/\mu m}$ in vertices (cc)	-	0.44±0.80	0.44±0.51

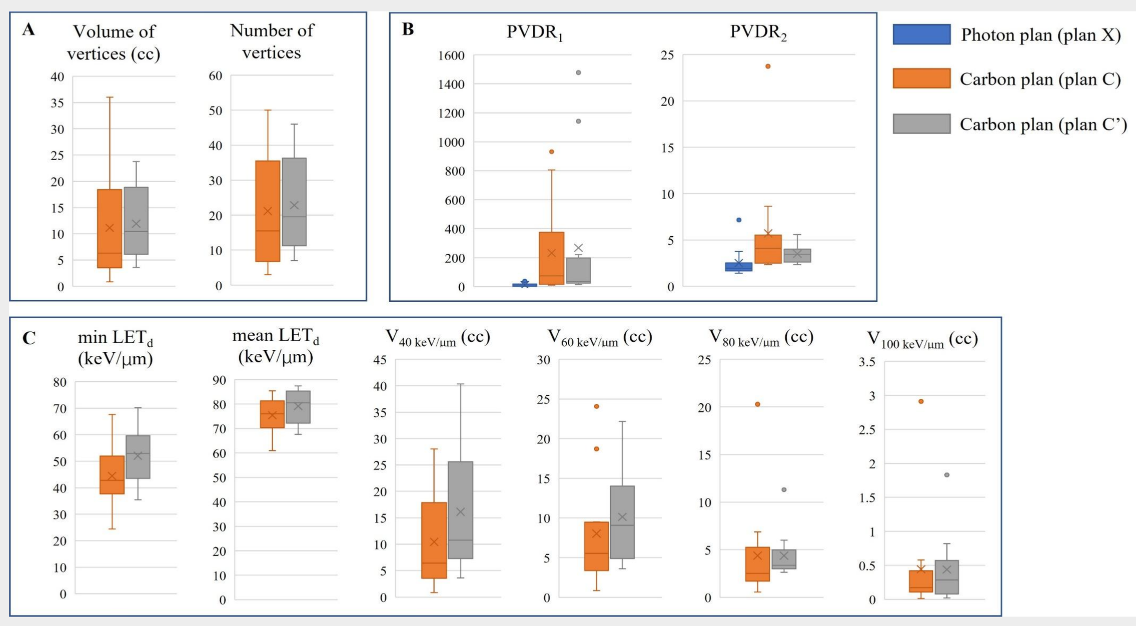

Figure 1. (A) Comparison for volume and number of vertices before and after lattice vertex arrangement optimization.
(B) Comparison of three plans for PVDR with two different definitions.
(C) Comparison for LET_d of carbon plans before and after arrangement optimization.

DISCUSSION

In this study, we conducted a comprehensive dosimetric comparison between photon- and heavy ion-based Lattice radiotherapy plans, and propose a novel vertex position optimization method to enhance the LETd within the vertices.
Due to the Bragg peak effect of carbon ions, a sharper dose distribution can be achieved in dosimetry compared with photons. Therefore, in SFRT, carbon ions can achieve a higher PVDR than photons, and better sparing of normal tissues. Doses to OARs adjacent to target area are substantially reduced relative to photon-based plans. Compared with photons, carbon ions have the potential to further increase the peak region under existing PVDR requirements or further enhance PVDR under existing peak volume. Although carbon ion SFRT has an exceptionally high PVDR and the potential to reduce the distance between vertex, using conventional photon-based vertex placement method is still a relatively safe choice in clinical practice at the current stage.
For a target with a certain three-dimensional volume, a single Bragg peak is insufficient to cover the entire thickness of the target area. Pencil beam scanning (PBS) rapidly switches between pencil beams of different energies and superimposes multiple Bragg peaks with varying energies and weights along the depth direction to generate a SOBP, ensuring sufficient irradiation of the target area. During SOBP construction, in order to achieve longitudinal broadening, a series of low-energy pencil beams must be introduced to cover the target from proximal to distal regions. While a single Bragg peak has a high LET at the peak position, the modulation

CONCLUSIONS

Carbon-ion plans significantly increased PVDR and reduced OAR doses relative to photon plans. The vertex-optimized strategy further elevated the minimum and mean LETd inside lattice peaks without degrading PVDRs or increasing normal-tissue exposure, achieving a precise "LET boost" within high-dose sub-volumes. These findings provide both dosimetric and radiobiological rationale for clinical translation of carbon-ion SFRT.

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