Physics and Imaging in Radiation Oncology 31 (2024) 100624

Contents lists available at ScienceDirect

Physics and Imaging in Radiation Oncology

journal homepage: www.sciencedirect.com/journal/physics-and-imaging-in-radiation-oncology

Original Research Article

Balancing benefits and limitations of linear energy transfer optimization in carbon ion radiotherapy for large sacral chordomas

Giovanni Parrella [a,*], Giuseppe Magro [b], Agnieszka Chalaszczyk [c], Marco Rotondi [d], Mario Ciocca [b], Lars Glimelius [d], Maria R. Fiore [c], Chiara Paganelli [a], Ester Orlandi [e,f], Silvia Molinelli [b,1], Guido Baroni [a,1]

[a] Department of Electronics, Information and Bioengineering, Politecnico di Milano, Via G.Ponzio 34/5, 20133 Milan, Italy
[b] Medical Physics Unit, National Center of Oncological Hadrontherapy (CNAO), Strada Campeggi, 53, 11 27100 Pavia, Italy
[c] Radiotherapy Unit, National Center of Oncological Hadrontherapy (CNAO), Strada Campeggi, 53, 11 27100 Pavia, Italy
[d] Raysearch Laboratories, Eugeniavägen 18, 113 68 Stockholm, Sweden
[e] Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Via A. Brambilla 74, 27100 Pavia, Italy
[f] Clinical Unit, National Center of Oncological Hadrontherapy (CNAO), Strada Campeggi, 53, 11 27100 Pavia, Italy

ARTICLE INFO

Keywords:
LET optimization
Carbon Ion Radiotherapy
Sacral Chordomas

ABSTRACT

Background and Purpose: A low linear energy transfer (LET) in the target can reduce the effectiveness of carbon ion radiotherapy (CIRT). This study aimed at exploring benefits and limitations of LET optimization for large sacral chordomas (SC) undergoing CIRT.

Materials and Methods: Seventeen cases were used to tune LET-based optimization, and seven to independently test interfraction plan robustness. For each patient, a reference plan was optimized on biologically-weighted dose cost functions. For the first group, 7 LET-optimized plans were obtained by increasing the gross tumor volume (GTV) minimum LET_d ($minLET_d$) in the range 37–55 keV/μm, in steps of 3 keV/μm. The optimal LET-optimized plan (LET_{OPT}) was the one maximizing LET_d, while adhering to clinical acceptability criteria. Reference and LET_{OPT} plans were compared through dose and LETd metrics (D_x, L_x to x% volume) for the GTV, clinical target volume (CTV), and organs at risk (OARs). The 7 held-out cases were optimized setting $minLET_d$ to the average GTV $L_{98\%}$ of the investigation cohort. Both reference and LET_{OPT} plans were recalculated on re-evaluation CTs and compared.

Results: GTV $L_{98\%}$ increased from (31.8 ± 2.5)keV/μm to (47.6 ± 3.1)keV/μm on the LET_{OPT} plans, while the fraction of GTV receiving over 50 keV/μm increased on average by 36% ($p < 0.001$), without affecting target coverage goals, or impacting LET_d and dose to OARs. The interfraction analysis showed no significant worsening with $minLET_d$ set to 48 keV/μm.

Conclusion: LET_d optimization for large SC could boost the LET_d in the GTV without significantly compromising plan quality, potentially improving the therapeutic effects of CIRT for large radioresistant tumors.

1. Introduction

When investigating particle beams in a clinical scenario, the dose-averaged linear energy transfer (LET_d) is a standard physical parameter that accounts for the mixed radiation field [1]. High-LET_d radiations such as carbon ions offer several advantages over photon and proton radiotherapy and are considered an alternative for the treatment of radioresistant targets such as sacral chordomas (SC) [2]. Currently, the local effect model (LEM I) and the modified microdosimetric kinetic model (mMKM) are the only two models used to estimate the relative biological effectiveness (RBE) in clinical practice for carbon ion radiotherapy (CIRT).

Despite both RBE models account for the entire LET spectrum, an equivalent RBE-weighted dose (D_{RBE}) can be achieved with both high and low LET radiations. When relying only on RBE-weighted dose objectives, the LET_d generally peaks at the distal edge of the spread-out

* Corresponding author at: Politecnico di Milano, Department of Electronics, Information and Bioengineering, via Giuseppe Colombo, 40 20133 Milano, Italy.
E-mail address: giovanni.parrella@polimi.it (G. Parrella).
[1] Shared last authorship.

https://doi.org/10.1016/j.phro.2024.100624
Received 28 February 2024; Received in revised form 2 August 2024; Accepted 4 August 2024
Available online 8 August 2024

Bragg peak (SOBP) of each beam, delivering most of the dose to the target through medium–low LET radiations. This effect becomes more evident for larger volumes, and consequently longer SOBP, and may reduce the radiobiological benefits of CIRT, possibly affecting treatment effectiveness for radioresistant tumors [3].

Multiple findings suggest that the standard approach of delivering a uniform RBE-weighted dose to the clinical target volume (CTV), may not be sufficient to guarantee local control. Indeed, a low-LET at the center of the gross tumor volume (GTV) is a potential negative prognostic factor. In particular, *in vitro* analyses suggest that the decrease in Oxygen Enhancement Ratio (OER) and increase of relative biological effectiveness start to be potentially relevant for LET values above 50 keV/μm [4,5]. As a result, boosting LET_d in the central portion of the target (i.e. GTV), where hypoxic areas are likely to exist, would most likely enhance treatment efficacy. Specifically, an investigation on sacral chordomas treated with CIRT highlighted how the fraction of GTV receiving at least 50 keV/μm ($V_{LET>50}$) was lower than 2% on average [3]. Similarly, a study on unresectable chondrosarcomas showed that cases with a near-to-minimum LET_d higher than 36.4 keV/μm in the planning target volume (PTV) experienced no recurrence [6]. An investigation performed on pancreatic cancer treated with CIRT suggested that achieving a minimum LET_d on the GTV greater than 44 keV/μm leads to a significantly higher local control [7]. Along with this, literature findings identified a correlation between tumor volume and the risk of local relapse (LR) [8,9] and a recent dosiomics study on SC treated with CIRT suggested LET_d as a possible source of prognostic factor to predict LR [10].

Given the relevance of these results, multiple approaches have been developed to enhance LET_d in the target or within hypoxic regions, such as simultaneous integrated boost (SIB), beams patching, LET- or kill-painting and multi-ions treatments [11–18]. In particular, LET_d optimization would allow integrating D_{RBE} and LET_d based objectives, potentially obtaining better solutions with respect to the conventional optimization [3,11]. At the time of this analysis, only one study reported on clinical application of LET_d optimization of carbon ion plans for head and neck tumors, with promising therapeutic effects [12,19]. A recent technical investigation on the use of LET_d based objectives (i.e. maximum and minimum LET_d) in a commercial treatment planning system (TPS) revealed a conflict between dose uniformity, plan robustness and LET_d maximization on the target, suggesting that the increase of LET_d on the tumor comes at the cost of either a lower plan robustness or a lower dose uniformity [20]. As most clinical scenarios require a uniform and robust dose coverage with respect to setup and range uncertainties, as well as sufficiently robust sparing of organs at risk (OAR), the feasibility of this new optimization approach should be investigated in a clinical setting. A recent work on sacral chordomas treated with CIRT investigated LET_d optimization applied to the CTV (median volume 454.9 cm^3), with promising results on plan robustness and OARs sparing [21].

In this context, our work evaluates benefits and limitations of LET_d optimization for treating large sacral chordomas with CIRT, extending the evaluation to larger target volumes with respect to [21] and thoroughly investigating the inter-fraction robustness of this approach.

2. Materials and methods

2.1. Patient cohort and treatment infrastructure

Twenty-four patients affected by non-metastatic SC and previously treated with CIRT at the National Centre for Oncological Hadrontherapy (CNAO) between 2013 and 2018 were selected for this study. The CTV was within the range [243, 2442]cm^3, with a median of 1135 cm^3 (Supplementary Table S1). The optimization analysis was performed on the first seventeen consecutively treated patients. The remaining seven, were selected among the patients having at least one re-evaluation CTs (CT_{rev}) to investigate inter-fraction robustness of the optimization approach on an independent population. In case of multiple CT_{rev} ($n = 1$) the latest CT_{rev} was considered, to account for the worst case. All patients signed an informed consent and data were anonymized accordingly. The study was approved by the local ethical committee (CNAO OSS 24/2021). Considering the use of different TPS for the optimization of the original plans, multiple prescription doses, organs at risk constraints and number of beams (Supplementary Table S2), all treatment plans were re-designed and optimized following the current clinical protocol at the institution.

2.2. Treatment optimization

The prescribed dose (D_p) was set to 73.6 Gy(RBE) to 50% of the CTV, delivered in 16 fractions using two fixed opposing lateral beams and one vertical beam, with the patient laying prone. The RBE was estimated with the LEM-I model, with $\alpha/\beta = 2$ Gy ($\alpha_x = 0.1$ Gy^{-1}, $\beta_x = 0.05$ Gy^{-2}, $D_t = 30$ Gy, $r = 5$ μm). The optimization was performed on a 3 mm dose grid, using the pencil beam dose engine v6.0 within a research version of RayStation 12B (RaySearch Laboratories, Sweden), with structure sets of the clinically delivered plan.

A reference plan was robustly optimized for each of the seventeen patients relying exclusively on RBE-weighted dose objectives, applying robust optimization criteria only to the CTV, bowel, sigma and rectum. The robustness included 28 different scenarios, as a result of the combination of 2 range (±3.5%) and 14 different setup (±5 mm) uncertainties. The plan was considered clinically acceptable if it met predetermined clinical goals for both CTV and surrounding OARs, including bowel, rectum, sigma, nerves and skin (Supplementary Table S3).

Then, seven plans for each patient were optimized by adding to the robust optimization above, a non-robust minimum LET_d ($minLET_d$) objective on the GTV. The seven $minLET_d$ values ranged from 37 to 55 keV/μm, with steps of 3 keV/μm. The lower bound (i.e. 37 keV/μm) was chosen as the median near to minimum LET_d (i.e. LET_d to 98% of the GTV, $L_{98\%}$) on the population, while the upper one (i.e. 55 keV/μm) was set to a reasonable maximum value defined experimentally after initial investigations, considering that LET_d above 50 keV/μm provide a more effective radiobiological benefit [5]. Each of the LET_d-optimized plans was tuned to satisfy all clinical goals on the nominal setting but did not necessarily satisfy the clinical goals for all the robust scenarios. The weight of the $minLET_d$ cost function was roughly corresponding to 50% of the weight applied to the CTV dose objectives and 30% of the OARs.

2.3. Treatment evaluation

A robust evaluation was performed on all plans, setting the range and setup margin uncertainty to 3% and 3 mm, and evaluating the pass rate of clinical goals over 28 scenarios. The plans were evaluated based on the cumulative dose volume histograms (DHV), considering the minimum dose to the 95%, 50% and 1% of the GTV and CTV (i.e. $D_{95\%}$, $D_{50\%}$ and $D_{1\%}$, respectively). The homogeneity index was calculated as $HI = (D_{2\%} - D_{98\%})/D_{50\%}$ [22].

The optimal LET_d-optimized plan (i.e. LET_{opt} plan) was defined for each patient as the one with the highest $minLET_d$ value that ensured a robust target coverage and OARs sparing. A plan was considered acceptable if it met specific criteria defined by a medical physics expert

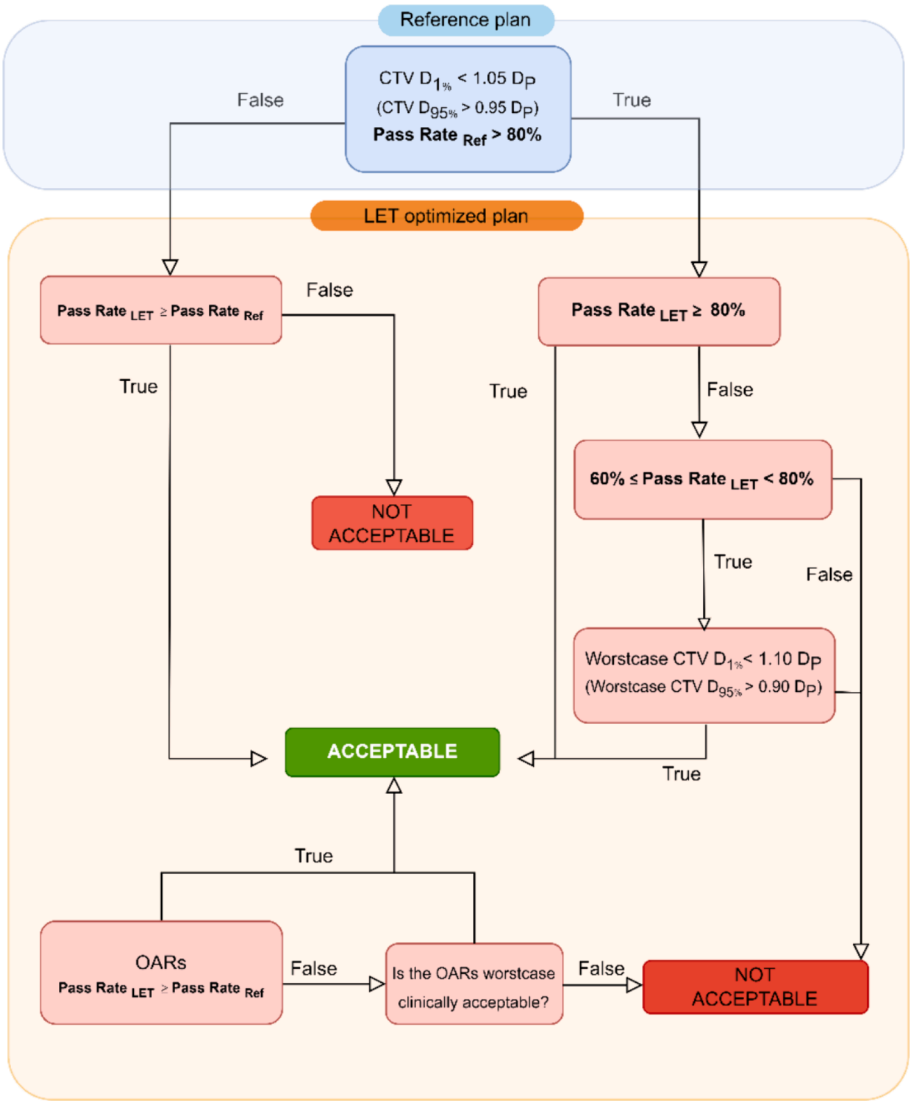

Fig. 1. Pipeline followed for the selection of the optimal LET_{opt} plan. A plan was considered acceptable only if both criteria on OARs and target coverage were respected.

and a radiation oncologist, as summarized in Fig. 1 and in Supplementary Section S3.

For each case, only the reference and the LET_{opt} plans were considered for further analyses.

Cumulative LET_d volume histogram (LVH) statistics describing the LET_d at 98% and 50% of the volume ($L_{98\%}$, $L_{50\%}$), as well as the volume receiving at least 50 keV/μm ($V_{LET>50}$) were used to compare each LET_{opt} plan to the corresponding reference one, for the GTV, CTV and OARs. The relationship between LET_d statistics and CTV volume was investigated through Spearman's correlation analysis. Downstream of the optimization, LET_d distributions were updated using the trichrome fragment spectra modelling and nuclear interaction correction [23] to guarantee a higher accuracy, especially in the OARs' metrics.

Both the reference and LET_{opt} plans were recalculated with the mMKM model ($\alpha_r = 0.764\ Gy^{-1}$, $\beta_r = 0.0615\ Gy^{-2}$, Clinical RBE factor = 2.41; cell type parameters: $\alpha_x = 0.172\ Gy^{-1}$, $\beta_x = 0.0615\ Gy^{-2}$, $r_{nucleus}$ = 3.9 μm) to address whether the LET_d optimization would affect dose discrepancies between the two RBE models, since a uniform LEM dose is generally not uniform when recomputed with the mMKM [24,25]. The two models were compared in terms of $D_{95\%}$ and $D_{50\%}$.

2.4. Inter-fraction evaluation

The same beam setting was applied to the seven held-out patients, and a reference plan based exclusively on dose objectives was optimized on the planning CT. Similarly, an additional plan was optimized including a non-robust $minLET_d$ objective function. The $minLET_d$ objective value was set to the average GTV $L_{98\%}$ (48 keV/μm) from the investigation cohort (n = 17). The CTV $D_{1\%}$ and $D_{95\%}$ were evaluated to determine a possible over/under dosage and assess the uniformity on the plan. The reference and LETopt plans were recalculated on the CTrev and compared in terms of dose uniformity and CTV metrics, to verify the inter-fraction robustness of LET_d–optimized plans, compared to the reference one.

The Mann–Whitney *U* test (α = 0.05) was applied to investigate statistically significant differences among the non-normally distributed metrics, defined with Shapiro's normality test (α = 0.05).

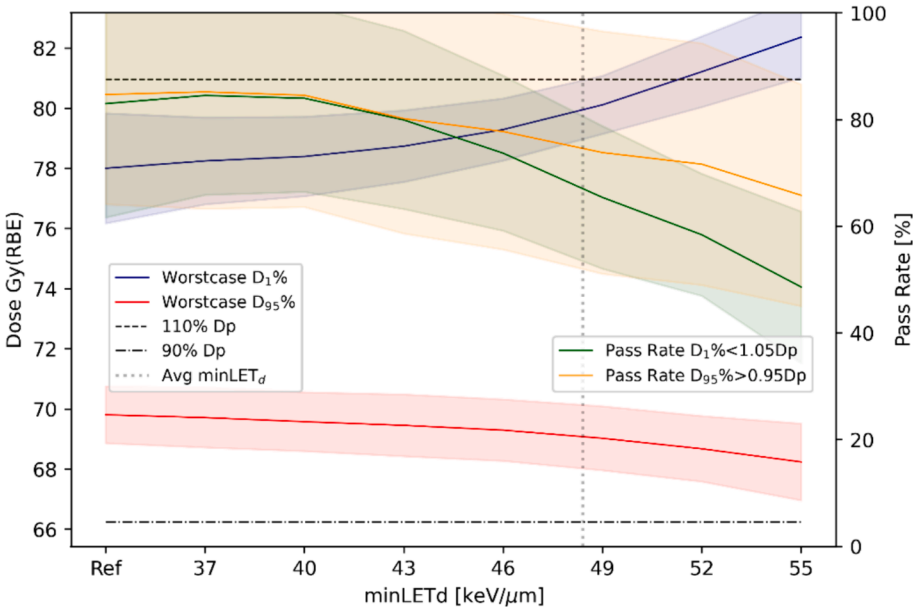

Fig. 2. The conflict between LET maximization, robustness and dose uniformity to the CTV (i.e $D_{1\%}$, $D_{95\%}$). Curves of worst-case CTV $D_{1\%}$ (blue) increase with increasing LET_d, while the worst-case CTV $D_{95\%}$ (red) decreases. In green, the rate of scenarios fulfilling $D_{1\%} < 1.05 \cdot D_p$, while in yellow the pass rate relative to $D_{95\%}$>0.95Dp, both referenced to the second vertical axis. All curves show the mean ± 1 standard deviation over the cohort (n = 17). The black dashed and dash-dotted horizontal lines show the dose limits for the worst-case dose, $1.10 \cdot D_p$ and $0.90 \cdot D_p$ respectively. The vertical dotted line represents the average GTV $L_{98\%}$ (48 keV/μm). On the x-axis, the values from the reference plan (i.e. no LET optimization), are denoted with "Ref". (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

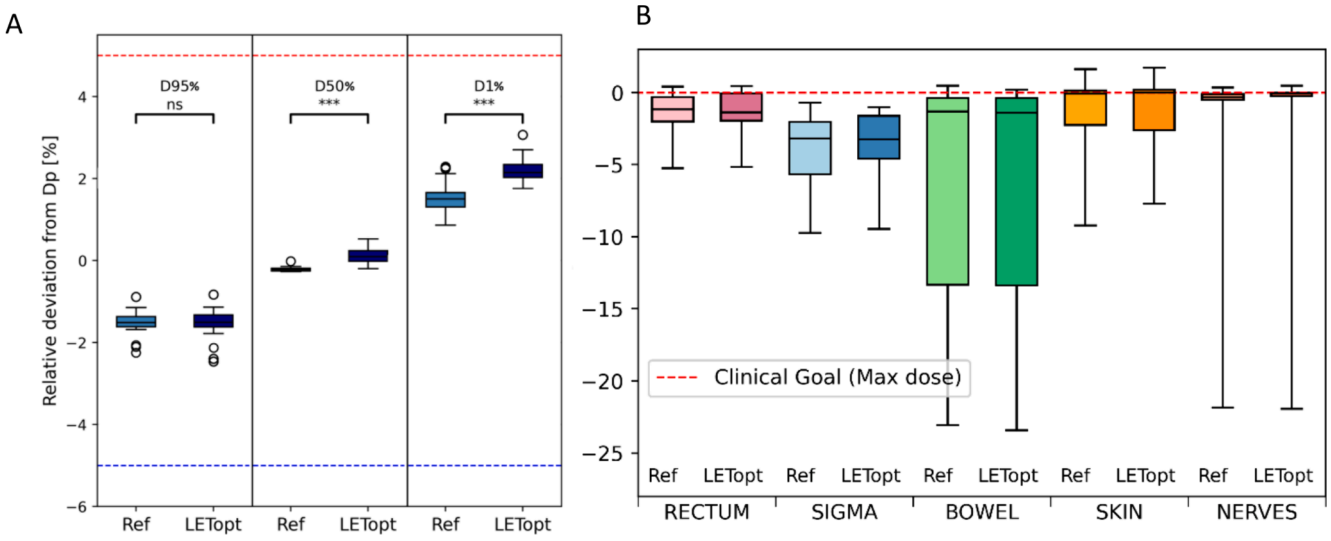

Fig. 3. A) Comparison of DVH metrics on the CTV between the reference and LET-optimized (LET_{opt}) nominal plans, over the entire cohort (n = 17), described as relative deviation from the prescription dose Dp = 73.6 Gy(RBE). The red and blue dashed lines show the ±5 % clinical margin. The boxplots show the median and IQR, while the whiskers include values up to 1.5 IQR. * = p-value < 0.05, ** = p-value < 0.01, *** = p-value < 0.001, ns = not significative. More details on p-values in Table 1. **B)** Dose margins on clinical goals for OARs on the nominal plans, computed as *Maximum dose − clinical goal*, for each OAR as in Table S3, for reference (Ref) and LET optimized plans (LET_{opt}). The red dashed line shows a zero relative deviation from each OAR's clinical goal, thus a negative margin represents a fulfilled clinical goal. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3. Results

A conflict was observed between maximizing the LET_d in the GTV, ensuring plan robustness and controlling the high- and low-dose regions to the CTV (i.e. $D_{95\%}$, $D_{1\%}$). Indeed, the worst-case CTV $D_{1\%}$ was observed to increase on average with increasing LET_d as shown in Fig. 2, while the worst-case $D_{95\%}$ was decreasing. In agreement with this, the average pass rate of $D_{1\%} < 1.05 \cdot D_p$ and $D_{95\%} > 0.95 \cdot D_p$ on the CTV decreased as LET_d increased. Dose uniformity on the nominal plan did not significantly degrade with the increase of LET_d, while the worst-case HI suffered a more relevant worsening, as shown in Supplementary Figure S1. Table S4 summarizes the optimal $minLET_d$ for each case.

By design, the reference and LET_{opt} plans were clinically acceptable in terms of robust target coverage and OARs sparing. The prescribed dose to the CTV was maintained within a ±5% tolerance range (Fig. 3A). All clinical goals for OARs were satisfied on the nominal plan (Fig. 3B), and showed a stable robustness with increasing LET_d, except for the skin and nerves that showed a slightly lower pass rate at high $minLET_d$

Table 1
DVH and LVH metrics from reference (Ref) and the optimal LET_d plans (LETopt), averaged over the investigation cohort (n = 17), for GTV and CTV. Mean ± std.dev. p-values relative to the Mann-Whitney *U* test (α = 0.05) between Ref and LETopt plans' metrics are shown for GTV and CTV.

		$D_{1\%}$	$D_{50\%}$	$D_{95\%}$	$L_{50\%}$	$L_{98\%}$	$V_{LET>50}$
		Gy(RBE)			keV/μm		%
GTV	**Ref**	74.5 ± 0.3	73.4 ± 0.1	72.4 ± 0.7	37.0 ± 2.0	31.8 ± 2.5	1.8 ± 1.9
	LET_{opt}	75.3 ± 0.3	74.1 ± 0.2	72.7 ± 0.	49.4 ± 2.9	47.6 ± 3.0	38.0 ± 46.5
	p-val	≪ 0.01	≪ 0.01	0.04	≪ 0.01	≪ 0.01	≪ 0.01
CTV	**Ref**	74.8 ± 0.3	73.4 ± 0.1	72.4 ± 0.2	38.0 ± 2.1	31.6 ± 2.3	5.0 ± 1.8
	LET_{opt}	75.3 ± 0.2	73.7 ± 0.1	72.4 ± 0.3	45.2 ± 3.0	34.0 ± 2.8	18.0 ± 20.3
	p-val	≪ 0.01	≪ 0.01	0.92	≪ 0.01	0.03	0.02

(Figure S2). For the skin, an overdosage of up to 3% was permitted in relation to the reference clinical goal. Dose and LET_d metrics for OARs are shown in Supplementary Figures S3, S4.

LET_d optimization significantly increased LET_d within the GTV and CTV ($p < 0.001$), as summarized in Table 1. In particular, GTV L_{98} increased from (31.8 ± 2.5) keV/μm to (47.6 ± 3.0) keV/μm, while $L_{50\%}$ from (37.0 ± 2.0) keV/μm to (49.4 ± 2.9) keV/μm (mean ± 1std.dev., Fig. 4). The $V_{LET>50}$ in the GTV increased on average by 36% ($p < 0.001$). Consequently, CTV $L_{50\%}$ increased from (38.0 ± 2.1) keV/μm to (45.2 ± 3.0) keV/μm and $L_{98\%}$ from (31.6 ± 2.3) keV/μm to (34.0 ± 2.8) keV/μm, as in Fig. 4. No correlation between $minLET_d$ values or LET_d metrics and CTV volumes was found (Spearman's C-index < 0.5). Patient specific results are summarized in Table S5.

The mMKM plan recalculations revealed that optimizing LET_d did not worsen the disparity between the two RBE models. On the contrary, LET_d optimization, on average, significantly improved the uniformity of mMKM plans from (0.12 ± 0.02) to (0.10 ± 0.01) and decreased the difference in GTV $D_{50\%}$ and $D_{95\%}$ by (1.6 ± 1.3) Gy(RBE) and (1.9 ± 1.3) Gy(RBE), respectively (Supplementary Fig. 5 and Figure S5).

The resulting average GTV L_{98} value (48 keV/μm) was set as the

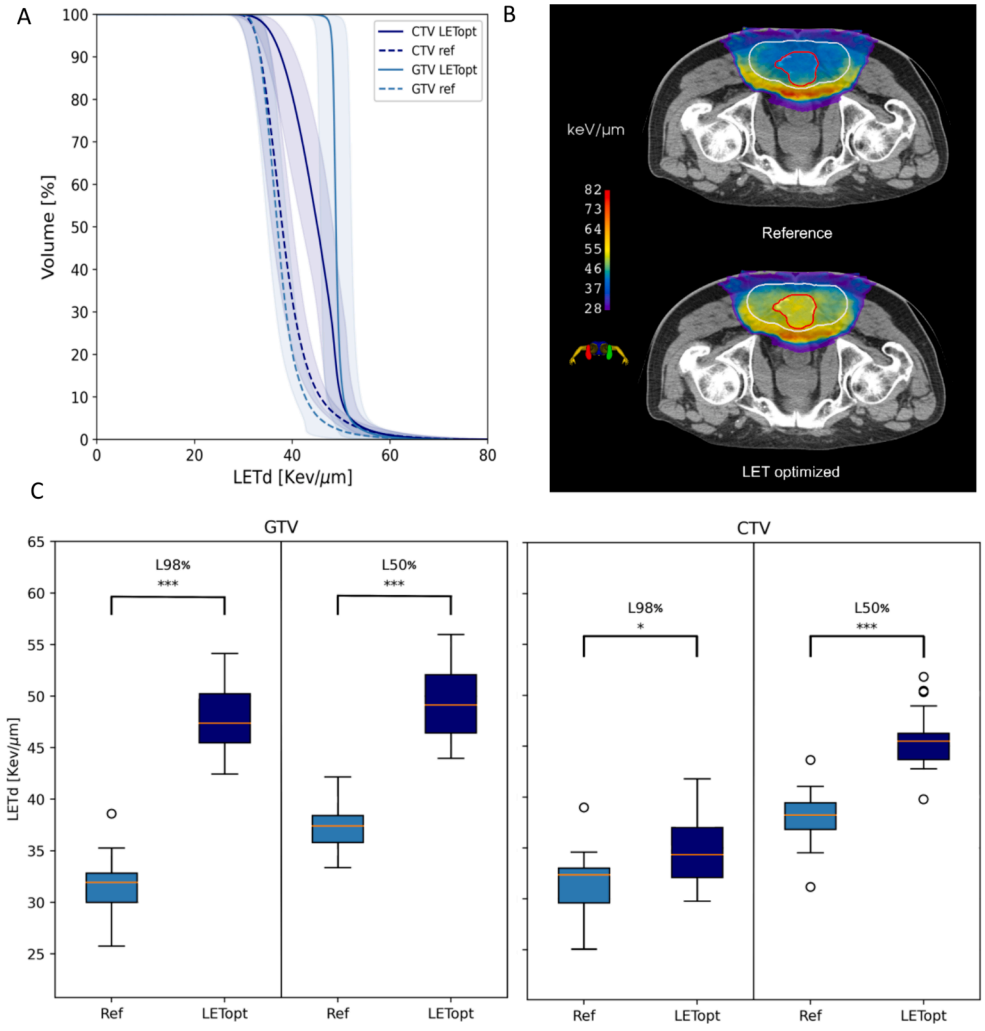

Fig. 4. A) Mean LVH ± 1 standard deviation over the investigation cohort (n = 17). **B)** Case example of LET_d distribution for a reference and LETopt plans. Axial view with contours of GTV (red) and CTV (white) **C)** LVH metrics relative to GTV (Left) and CTV (Right), compared between LET optimized (LET_{opt}) and reference plans (Ref). The boxplot shows the median and IQR, while the whiskers include values up to 1.5 IQR. * = p-value < 0.05, ** = p-value < 0.01, *** = p-value < 0.001. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

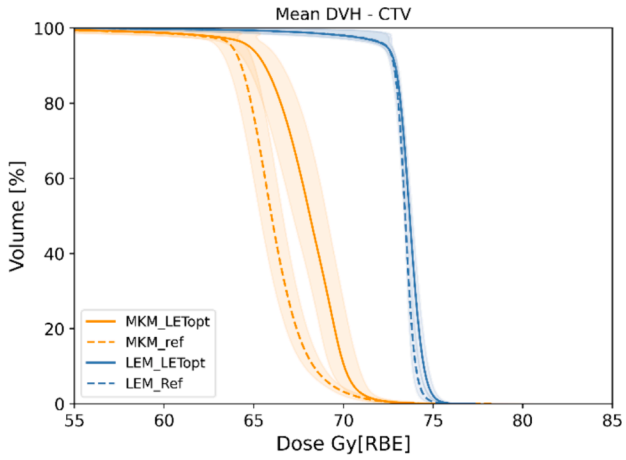

Fig. 5. Comparison of LEM and MKM mean DVH curves in the reference (ref) and LET optimized (LETopt) plans for the CTV. All curves show the mean ± 1 standard deviation over the cohort (n = 17).

$minLET_d$ objective value on the hold-out patients. On average, the reference and LET_d optimized plans showed no under/over dosage (i.e. $D_{1\%}$<1.05·Dp and $D_{95\%}$>0.95·Dp), as well as a clinically acceptable OARs sparing when computed on the re-evaluation CTs. GTV $L_{98\%}$ increased on average from (33.5 ± 1.3) keV/μm to (47.8 ± 0.3) keV/μm in the LET_d plans computed on the planning CTs, while CTV $L_{98\%}$ increased from (34.2 ± 1.3) keV/μm to (41.4 ± 4.2) keV/μm.

The analysis on DVH metrics between recalculations on CT_{rev} and the plans optimized on planning CT revealed no statistically significant discrepancies between the two sets of plans ($p > 0.05$, Supplementary Figure S6).

4. Discussion

This study examined the advantages and limitations of LET_d optimization for treating large sacral chordomas with CIRT by evaluating it over the entire treatment and accounting for inter-fraction robustness. Specifically, we analyzed how increasing the minimum LET_d in the GTV could impact the quality of the treatment plan in terms of robustness and adherence to clinical goals for OARs. This analysis confirmed the conflict between plan robustness, LET_d maximization and dose uniformity observed by Friedriksson et al. [20]. Notably, an increase in high −dose regions within the target volume may be of major concern for clinical applications, as the maximum dose showed a substantial rise with increasing LET_d (Fig. 2). Similarly, an increased presence of low-dose regions in the target was noticed with increasing LET_d, at a lower degree, describing an overall decreased plan robustness and uniformity. Nonetheless, the dose coverage on the nominal plan remained stable.

Optimizing LET_d led to a significant boost in GTV $L_{98\%}$ and $L_{50\%}$ values, which increased on average by (15.8 ± 5.5) keV/μm and (12.4 ± 4.9) keV/μm, respectively. Additionally, the fraction of GTV exposed to high-LET_d radiation ($V_{LET>50}$) increased from 1.8% to 38.0%, on average. This outcome holds particular significance considering Matsumoto et al.'s findings, which indicate that no recurrences occurred for $V_{LET>50}$ values exceeding 44 % in patients with unresectable chondrosarcomas treated with CIRT [6]. The average near-to-minimum CTV LET_d ($L_{98\%}$) increased from (31.6 ± 2.3) keV/μm to (34.0 ± 2.8) keV/μm, approaching the value described by Matsumoto (36.4 keV/μm) for preventing relapses in radioresistant tumors with a volume, on average, half-size of the median target in our population [6]. Hagiwara and colleagues found a positive correlation between minimum LET_d in the GTV exceeding 44 keV/μm and LC in pancreatic cancer treated with CIRT, highlighting the clinical relevance of our GTV $L_{98\%}$ enhancement to (47.6 ± 3.0) keV/μm [7]. These findings align with a recent work on SC treated with CIRT that investigated an alternative approach to LET_d maximization on the CTV using beam patching, achieving a high-dose CTV (HD-CTV) $L_{50\%}$ of (47 ± 8.1) keV/μm. Moreover, a recent publication on LET_d optimization on the HD-CTV of SC reported comparable results on smaller irradiated volumes reaching a HD-CTV $L_{50\%}$ of (47.9 ± 2.2) keV/μm, without compromising the OARs and plan robustness. In particular, LET_d was optimized considering a $minLET_d$ of 60 keV/μm over 7 of 16 fractions, to mitigate the effects on plan robustness.

Our results suggest that LET_d maximization in the GTV could significantly increase the LET_d in the central hypoxic region of the target, without substantially compromising plan robustness. Robustness was evaluated considering the fraction of scenarios fulfilling clinical goals rather than solely the worst-case, to avoid an overly pessimistic approach. Furthermore, the recalculation of LET_d plans on the CT_{rev} showed no variation in terms of inter-fraction robustness, when compared to the reference plan. A $minLET_d$ value of 48 keV/μm on the GTV, could be the starting point for plan optimization in large chordoma patients treated with CIRT. Nonetheless, the limited patient cohort size, due to the extremely low incidence of SC and the computational demand of this work, should be considered when interpreting these results.

LET_d optimization significantly reduced the discrepancy between mMKM and LEM-I, which model the RBE-LET dependence differently. LEM-I underestimates RBE in high-LET regions [26,27]; thus, higher LET_d in the target causes an increased recalculated MKM dose compared to the reference plan (Fig. 5). Moreover, the shorter SOBP modulation region achieved through LET_d maximization on the GTV reduced the cold and hot spots observed in mMKM recalculations and resulted in a closer agreement between the two models, potentially reducing the associated clinical risks.

Despite the promising findings, there is still no definitive consensus on which LET_d parameter is more closely associated with clinical outcomes and should be prioritized to enhance treatment effectiveness [3,6,7,10]. Indeed, there is a rising interest in a new dosimetric quantity that represents the dose delivered by high-LET radiations, that might be relevant to the treatment effectiveness and thus treatment optimization for SC [28]. Future studies may investigate the concomitant use of LET_d objectives on different ROIs, or the development of LVH-related cost functions. Additionally, while no correlation was observed between the selection of the optimal $minLET_d$ and the CTV volume, these findings cannot be generalized to all SC. Smaller tumors might benefit from higher LET_d levels in the target, necessitating further investigations. A recent prospective study on LET painting for head and neck tumors (GTV volume<150 cm^3) observed a $minLET_d$ increase from 53 to 64 keV/μm within the GTV with an associated increased therapeutic effect (i.e. 67 % tumor control, against 56 %) after 180 days [25].

In future applications, the use of a gantry might improve treatment outcomes by providing more degrees of freedom in the optimization, compared to the fixed 3-beams configuration employed in this analysis. Moreover, the dependence of RBE dose and LET_d distribution on the specific treatment design partially limits the generalizability of these findings, but it does not undermine the overall insights gained [27].

This study serves as a foundation for the implementation of LET_d optimization in clinical practice, while also identifying its benefits and critical aspects. Furthermore, it presents promising findings towards a significantly improvement of CIRT treatments for large SC patients.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This research was funded by AIRC (Associazione Italiana per la Ricerca sul Cancro), grant number IG2020-24946. The authors would like to thank Maksym Hladchuk for supporting data analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.phro.2024.100624.

References

[1] Kalholm F, Grzanka L, Traneus E, Bassler N. A systematic review on the usage of averaged LET in radiation biology for particle therapy. Radiother Oncol 2021;161:211–21. https://doi.org/10.1016/j.radonc.2021.04.007.

[2] Dong M, Liu R, Zhang Q, Wang D, Luo H, Wang Y, et al. Efficacy and safety of carbon ion radiotherapy for chordomas: a systematic review and meta-analysis. Radiat Oncol 2023;18:152. https://doi.org/10.1186/s13014-023-02337-x.

[3] Molinelli S, Magro G, Mairani A, Allajbej A, Mirandola A, Chalaszczyk A, et al. How LEM-based RBE and dose-averaged LET affected clinical outcomes of sacral chordoma patients treated with carbon ion radiotherapy. Radiother Oncol 2021;163:209–14. https://doi.org/10.1016/j.radonc.2021.08.024.

[4] Tinganelli W, Durante M. Carbon ion radiobiology. Cancers 2020;12:3022. https://doi.org/10.3390/cancers12103022.

[5] Furusawa Y, Fukutsu K, Aoki M, Itsukaichi H, Eguchi-Kasai K, Ohara H, et al. Inactivation of aerobic and hypoxic cells from three different cell lines by accelerated 3He-, 12C- and 20Ne-Ion beams. Radiat Res 2000;154:485–96. https://doi.org/10.1667/0033-7587(2000)154[0485:ioaahc]2.0.co;2.

[6] Matsumoto S, Lee SH, Imai R, Inaniwa T, Matsufuji N, Fukahori M, et al. Unresectable chondrosarcomas treated with carbon ion radiotherapy: relationship between dose-averaged linear energy transfer and local recurrence. Anticancer Res 2020;40:6429–35. https://doi.org/10.21873/anticanres.14664.

[7] Hagiwara Y, Bhattacharyya T, Matsufuji N, Isozaki Y, Takiyama H, Nemoto K, et al. Influence of dose-averaged linear energy transfer on tumour control after carbon-ion radiation therapy for pancreatic cancer. Clin Transl Radiat Oncol 2020;21:19–24. https://doi.org/10.1016/j.ctro.2019.11.002.

[8] Bostel T, Mattke M, Nicolay NH, Welzel T, Wollschläger D, Akbaba S, et al. High-dose carbon-ion based radiotherapy of primary and recurrent sacrococcygeal chordomas: long-term clinical results of a single particle therapy center. Radiat Oncol 2020;15:206. https://doi.org/10.1186/s13014-020-01647-8.

[9] Reiko I, Tadashi K, Nobuhito A. Clinical efficacy of carbon ion radiotherapy for unresectable chondrosarcomas. Anticancer Res 2017;37. https://doi.org/10.21873/anticanres.12162.

[10] Morelli L, Parrella G, Molinelli S, Magro G, Annunziata S, Mairani A, et al. A dosiomics analysis based on linear energy transfer and biological dose maps to predict local recurrence in sacral chordomas after carbon-ion radiotherapy. Cancers 2022;15:33. https://doi.org/10.3390/cancers15010033.

[11] Bassler N, Toftegaard J, Lühr A, Sørensen BS, Scifoni E, Krämer M, et al. LET-painting increases tumour control probability in hypoxic tumours. Acta Oncol 2014;53:25–32. https://doi.org/10.3109/0284186X.2013.832835.

[12] Kohno R, Koto M, Ikawa H, Lee SH, Sato K, Hashimoto M, et al. High–linear energy transfer irradiation in clinical carbon-ion beam with the linear energy transfer painting technique for patients with head and neck cancer. Adv Radiat Oncol 2023:101317. https://doi.org/10.1016/j.adro.2023.101317.

[13] Fager M, Toma-Dasu I, Kirk M, Dolney D, Diffenderfer ES, Vapiwala N, et al. Linear energy transfer painting with proton therapy: a means of reducing radiation doses with equivalent clinical effectiveness. Int J Radiat Oncol Biol Phys 2015;91:1057–64. https://doi.org/10.1016/j.ijrobp.2014.12.049.

[14] Giantsoudi D, Grassberger C, Craft D, Niemierko A, Trofimov A, Paganetti H. Linear energy transfer-guided optimization in intensity modulated proton therapy: feasibility study and clinical potential. Int J Radiat Oncol Biol Phys 2013;87:216–22. https://doi.org/10.1016/j.ijrobp.2013.05.013.

[15] Malinen E, Søvik Å. Dose or 'LET' painting – What is optimal in particle therapy of hypoxic tumors? Acta Oncol 2015;54:1614–22. https://doi.org/10.3109/0284186X.2015.1062540.

[16] Sokol O, Krämer M, Hild S, Durante M, Scifoni E. Kill painting of hypoxic tumors with multiple ion beams. Phys Med Biol 2019;64:045008. https://doi.org/10.1088/1361-6560/aafe40.

[17] Sokol O, Durante M. Carbon ions for hypoxic tumors: are we making the most of them? Cancers (Basel) 2023;15:4494. https://doi.org/10.3390/cancers15184494.

[18] Nachankar A, Schafasand M, Carlino A, Hug E, Stock M, Góra J, et al. Planning strategy to optimize the dose-averaged LET distribution in large pelvic sarcomas/chordomas treated with carbon-ion radiotherapy. Cancers 2023;15:4903. https://doi.org/10.3390/cancers15194903.

[19] Koto M, Ikawa H, Inaniwa T, Imai R, Shinoto M, Takiyama H, et al. Dose-averaged LET optimized carbon-ion radiotherapy for head and neck cancers. Radiother Oncol 2024;194:110180. https://doi.org/10.1016/j.radonc.2024.110180.

[20] Fredriksson A, Glimelius L, Bokrantz R. The LET trilemma: conflicts between robust target coverage, uniform dose, and dose-averaged LET in carbon therapy. Med Phys 2023 Dec;50(12):7338–48. https://doi.org/10.1002/mp.16771.

[21] Schafasand M, Resch AF, Nachankar A, Góra J, Martino G, Traneus E, et al. Dose averaged linear energy transfer optimization for large sacral chordomas in carbon ion therapy. Med Phys 2024. https://doi.org/10.1002/mp.17102.

[22] The International Commission on Radiation Units and Measurements. J ICRU 2010;10:NP.2-NP. https://doi.org/10.1093/jicru/ndq001.

[23] Bazani A, Brunner J, Russo S, Carlino A, Simon Colomar D, Ikegami Andersson W, et al. Effects of nuclear interaction corrections and trichrome fragment spectra modelling on dose and linear energy transfer distributions in carbon ion radiotherapy. Phys Imaging Radiat Oncol 2024;29:100553. https://doi.org/10.1016/j.phro.2024.100553.

[24] Fossati P, Molinelli S, Matsufuji N, Ciocca M, Mirandola A, Mairani A, et al. Dose prescription in carbon ion radiotherapy: a planning study to compare NIRS and LEM approaches with a clinically-oriented strategy. Phys Med Biol 2012;57:7543–54. https://doi.org/10.1088/0031-9155/57/22/7543.

[25] Mein S, Klein C, Kopp B, Magro G, Harrabi S, Karger CP, et al. Assessment of RBE-weighted dose models for carbon ion therapy toward modernization of clinical practice at HIT. In vitro, in vivo, and in patients. Int J Radiat Oncol Biol Phys 2020;108:779–91. https://doi.org/10.1016/j.ijrobp.2020.05.041.

[26] Elsässer T, Krämer M, Scholz M. Accuracy of the local effect model for the prediction of biologic effects of carbon ion beams in vitro and in vivo. Int J Radiat Oncol Biol Phys 2008;71:866–72. https://doi.org/10.1016/j.ijrobp.2008.02.037.

[27] Góra J, Grosshagauer S, Fossati P, Mumot M, Stock M, Schafasand M, Carlino A. The sensitivity of radiobiological models in carbon ion radiotherapy (CIRT) and its consequences on the clinical treatment plan: differences between LEM and MKM models. J Appl Clin Med Phys 2024;25(7):e14321. https://doi.org/10.1002/acm2.14321.

[28] Schafasand M, Resch AF, Nachankar A, Gora J, Traneus E, Glimelius L, et al. Investigation on the physical dose filtered by linear energy transfer for treatment plan evaluation in carbon ion therapy. Med Phys 2024;51(1):556–65. https://doi.org/10.1002/mp.16751.