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Reoptimization of intensity-modulated proton therapy plans based on linear energy transfer

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Abstract

Purpose—We describe a treatment plan optimization method for intensity-modulated proton therapy (IMPT) that avoids high values of linear energy transfer (LET) in critical structures located within or near the target volume, while limiting degradation of the best possible physical dose distribution.

Methods—To allow fast optimization based on dose and LET, a GPU-based Monte-Carlo code was extended to provide dose-averaged LET in addition to dose for all pencil beams. After optimizing an initial IMPT plan based on physical dose, a prioritized optimization scheme is used to modify the LET distribution while constraining the physical dose objectives to values close to the initial plan. The LET optimization step is performed based on objective functions evaluated for the product of LET and physical dose (LETxD). To first approximation, LETxD represents a measure of the additional biological dose that is caused by high LET.

Results—The method is effective for treatments where serial critical structures with maximum dose constraints are located within or near the target. We report on 5 patients with intra-cranial tumors (high-grade meningiomas, base-of-skull chordomas, ependymomas) where the target volume overlaps with the brainstem and optic structures. In all cases, high LETxD in critical structures could be avoided while minimally compromising physical dose planning objectives.

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Conflicts of interest:

None

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Conclusion—LET-based reoptimization of IMPT plans represents a pragmatic approach to bridge the gap between purely physical dose-based and RBE-based planning. The method makes IMPT treatments safer by mitigating a potentially increased risk of side effects due to elevated relative biological effectiveness (RBE) of proton beams near the end of range.

Introduction

In-vitro cell survival experiments suggest an increase in proton relative biological effectiveness (RBE) towards the end of range. Although the data from in-vitro experiments varies substantially, it suggests that, depending on the dose and the tissue parameters, the RBE might increase from values between 1.0 and 1.1 in the entrance region to values around 1.3 at the Bragg peak and 1.6 in the falloff region [1]. It is typically assumed that this RBE increase is explained by an increase of linear energy transfer (LET) towards the end of range. On the other hand, proton treatment planning and dose reporting has been based on physical dose and a constant RBE of 1.1.

This creates a dilemma for proton therapy planning, especially for IMPT. Underestimation of RBE may lead to underestimation of normal tissue complication probabilities. IMPT treatments with highly modulated fields may deliver highly inhomogeneous LET distributions. This may result in LET hot spots in critical structures within or near the target volume, with LET values higher than those observed for passive scattering or single field uniform dose (SFUD) treatments. On the other hand, large uncertainties in endpoint-specific RBE values, and the fact that dose reporting has historically been based on physical dose, discourage RBE-based IMPT planning approaches that lead to drastic changes compared to current practice.

Previous works have investigated IMPT optimization based on biological dose instead of physical dose [2,3]. However, such approaches are yet to be adopted clinically. If treatment planning objectives for target coverage are evaluated only in terms of biological dose, such methods typically lead to lower physical doses in parts of the target, based on the assumption that the RBE is larger than 1.1 in areas of high LET. There is a danger that this could lead to target under-dosage if the RBE is overestimated. Other authors have redressed this issue by combining physical dose optimization with the goal of additionally influencing the LET distribution [4–8]. Most works [4–6] focus on increasing LET in radioresistant tumors to achieve a higher biological effect.

Unlike previous studies, our work is primarily concerned with the risk of normal tissue complications. We introduce a hybrid method between physical dose and LET-based IMPT planning. In contrast to previous works, our method does not assume knowledge of RBE to perform biological IMPT planning. Instead, it is designed to facilitate IMPT planning in the absence of reliable normal tissue RBE values. We first determine an IMPT plan based on physical dose objectives, as is current clinical practice. In a second step, we modify the LET distribution to avoid high LET in critical structures. This is done using a prioritized optimization scheme [9,10], in which LET-based objectives are optimized while limiting the degradation of the physical dose distribution. In that sense, IMPT treatment plans become safer, while allowing the planning process to be consistent with current dose reporting.

Methods

Patients

We reviewed patients with intra-cranial tumors that were treated using passively scattered proton beams at our institution. For this study, we selected cases where the clinical target volume was directly adjacent or overlapping with serial organs at risk (OARs), i.e. structures where the risk of side effects mainly depends on the maximum dose. We discuss 3 selected patients in detail: an atypical meningioma case where the target volume overlays the brainstem, optic nerve, chiasm, and the pituitary gland (Figure 1a), an ependymoma case for which the target volume involves parts of the brainstem (Figure 3a), and a base-of-skull chordoma case where the target abuts the brainstem (Figure 4a). Results for 2 additional patients (1 ependymoma, 1 base-of-skull chordoma) are presented in the supplementary material (Appendix D). For the current study, these patients were re-planned for IMPT using the beam directions from the clinically delivered treatment. The pencil beam sizes used represent the latest generation of proton machines (2.2–5.6 mm sigma at isocenter in air for energies of 230–60 MeV). For all cases, gross tumor volume (GTV) and clinical target volume (CTV) were taken from the clinical treatment plan. An isotropic 2 mm margin was added to the CTV to obtain a planning target volume (PTV) for IMPT planning.

Parameterization of biological effects

We consider the exponential cell survival model

$$S = \exp(-\alpha d) \quad (1)$$

where d is the physical dose and S is the surviving fraction of cells. To a first approximation, it is assumed [11–14] that the radiosensitivity parameter α increases linearly with dose-averaged LET, which we denote by L :

$$\alpha = \alpha_0 (1 + cL) \quad (2)$$

In analogy to the biologically effective dose (BED) model, the total biological dose b can be defined as

$$b = -\log(S)/\alpha_0 = (1 + cL) d = d + cLd \quad (3)$$

Hence, the product of LET and dose, scaled by a parameter c , can be interpreted as the additional biological dose due to the LET effect, which is added to the physical dose to obtain the total biological dose b . Alternatively, $(1 + cL)$ can be interpreted as the RBE, so that b represents the RBE-weighted dose (see discussion in the supplementary material, Appendix A).

For IMPT planning, the biological dose model is extended to multiple pencil beams. Let $D_{ij}x_j$ denote the physical dose that pencil beam j delivers to voxel i . Here, D_{ij} denotes the dose contribution of pencil beam j to voxel i for unit fluence, and x_j denotes the fluence of pencil beam j . The total cell survival in voxel i is given by

$$S_i = \prod_j \exp(-\alpha_0 (1 + cL_{ij}) D_{ij}x_j) \quad (4)$$

where L_{ij} is the dose-averaged LET of pencil beam j in voxel i . The RBE-weighted dose is thus given by

$$b_i = -\frac{\log(S_i)}{\alpha_0} = \sum_j (1 + cL_{ij}) D_{ij}x_j = d_i + c \sum_j L_{ij} D_{ij}x_j \quad (5)$$

where d_i is physical dose in voxel i . By defining the dose-averaged LET over all pencil beam contributions as

$$\bar{L}_i = \frac{\sum_j L_{ij} D_{ij}x_j}{d_i} \quad (6)$$

the biological extra dose due to the LET effect is given by the product of physical dose and dose-averaged LET, $c\bar{L}_i d_i$. The calculation of dose and LET contributions, D_{ij} and L_{ij} , is performed using a fast GPU-based Monte-Carlo code [15,16] as detailed in the supplementary materials (Appendix B). Given dose coefficients D_{ij} and LET coefficients L_{ij} , the additional biological dose due to elevated LET is a linear function of the optimization variables x_j . Hence, the same mathematical optimization techniques as in physical dose optimization can be applied.

Treatment plan optimization

In order to perform treatment planning consistent with current clinical practice, we first optimize an IMPT plan based on physical dose. We use the following objectives:

1. Deliver a prescribed physical dose of 50 Gy to the target volume, and penalize dose above 52.5 Gy (implemented via quadratic penalty functions).
2. Penalize dose above 50 Gy in OARs (optic structures, brainstem, pituitary gland) (implemented via quadratic penalty functions).
3. Conformity (implemented via quadratic penalty functions with a maximum dose that depends linearly on the distance from the target).

4. Minimize the generalized equivalent uniform dose (gEUD) in the brainstem.
5. Minimize the mean dose in the brain.

The details of treatment plan optimization can be found in the supplementary material (Appendix C.1). This initial step yields a plan that is optimal in terms of the chosen physical dose objectives, which we refer to as the *reference plan* below.

In the second step, the plan is adjusted in order to avoid high values of $\bar{L}_i d_i$ in the brainstem and other OARs. This is performed using a prioritized optimization scheme [9,10], i.e. a second IMPT optimization problem is solved where all physical dose planning goals are handled through constraints. In our application, target coverage should not be compromised. Also, the physical dose in OARs should not increase above 50 Gy, and conformity should not deteriorate. Hence, the values of objectives 1, 2 and 3 are constrained to the optimal value in the reference plan. However, it is expected that plan modifications will lead to small increases in integral dose and the brainstem gEUD. We therefore allow a 3% increase for objectives 4 and 5.

The only objective in the second IMPT optimization problem is to reduce $\bar{L}_i d_i$ in the OARs (brainstem, optic structures, pituitary gland). This can be done using quadratic penalty functions that penalize $\bar{L}_i d_i$ values that are higher than the minimum value that can realistically be achieved for the given prescription dose. In order to obtain such a minimum value, we consider the histogram of $\bar{L}_i d_i$ values in the target volume for the reference plan. We determine a threshold value $L d^{\text{ref}}$ such that 95% of the target volume receives $\bar{L}_i d_i$ values higher than $L d^{\text{ref}}$. We then introduce the objective function

$$f_L = \sum_{i \in \text{OARs}} \left(\bar{L}_i d_i - L d^{\text{ref}} \right)_+^2 \quad (7)$$

which is minimized to obtain the final treatment plan (see the supplementary material, Appendix C.2 for details).

Visualizing LETxD distributions

The treatment planning approach as described above does not require any quantification of RBE effects, i.e. the parameter c that scales the biological dose contribution $\bar{L}_i d_i$ does not have to be known. However, for visualization and estimating the potential benefit of LET redistribution, it is useful to select the parameter c so that $d_i + c \bar{L}_i d_i$ reflects an estimate of the RBE-weighted dose. For this work, we set $c = 0.04 \mu\text{m/keV}$, which yields a RBE of 1.1 in the center of a spread-out Bragg peak of 5 cm modulation and 10 cm range where the dose-averaged LET is approximately $\bar{L} \approx 2.5 \text{ keV/}\mu\text{m}$. For a pristine Bragg peak this corresponds to an RBE of approximately 1.3 at the Bragg peak (see illustration in the supplementary material, Appendix B).

Although difficult to verify for clinically relevant endpoints in normal tissues, it has been hypothesized that the RBE increase with LET is steeper for normal tissues with low α/β -values than for tumors with higher α/β -values. Therefore, the RBE-weighted dose resulting from $c = 0.04 \mu\text{m/keV}$ can be considered as a reference point, but the RBE may be higher by an unknown amount. For example, at a dose of 1.67 Gy per fraction (50 Gy in 30 fractions), the RBE model by McNamara [13] predicts an approximately linear increase of RBE with LET corresponding to $c \approx 0.02 \mu\text{m/keV}$ for $\alpha/\beta=10$ and $c \approx 0.05 \mu\text{m/keV}$ for $\alpha/\beta=2$.

Results

Atypical meningioma (case 1)

We first illustrate the method for the meningioma patient shown in Figure 1a. Figures 1c shows the physical dose distribution of the reference plan, and Figure 1e the corresponding LETxD distribution reflecting the extra biological dose due to elevated LET. The average value of $c\bar{L}_i d_i$ in the target volume is 5.8 Gy (for $c = 0.04 \mu\text{m/keV}$). However, in the high dose region of the brainstem, the pituitary gland, the chiasm, and the optic nerve, $c\bar{L}_i d_i$ reaches values of approximately 12 Gy, corresponding to RBE-weighted doses exceeding 60 Gy. If the value $c = 0.04 \mu\text{m/keV}$ underestimates the LET effect on RBE in these critical structures, the RBE-weighted dose will be even higher.

Figures 1d and 1f show the reoptimized treatment plan that penalizes $c\bar{L}_i d_i$ values in critical structures exceeding $Ld^{\text{ref}} = 3.8$ Gy. Figure 1f demonstrates that LETxD hotspots in OARs are avoided; LETxD is reduced to values close to the mean target LETxD of 5.8 Gy. Corresponding dose-volume histograms (DVH) evaluated for LETxD confirm the reduction in LETxD in OARs (Figure 2b). Table 1 quantifies the LETxD reductions in the brainstem for specific DVH points. Figures 1d and 2a confirm that the physical dose distribution in the vicinity of the target is close to the reference plan as enforced by the constraints.

It is clear that, in order to modify the LETxD distribution in critical structures, the dose to these regions has to be delivered by different pencil beams. This is illustrated in Figure 1b, which shows the difference between the physical dose distributions (the reoptimized plan is subtracted from the reference plan). The fluence of pencil beams incident from the patient's left (right side of the image) that stop in the OARs is reduced. Instead, more dose is delivered by pencil beams incident from the patient's right (left side of the image).

Ependymoma (case 2)

Figure 3 shows results for an ependymoma case where the target volume includes parts of the brainstem. In the reference treatment plan, elevated LETxD values are observed in the brainstem (Figure 3e). After reoptimization, LETxD hot spots in the brainstem can be avoided (Figure 3f). Figure 3b illustrates how the LETxD distribution is modified. The reference plan heavily uses pencil beams from the left-posterior beam (right side of the image) that stop within the brainstem. The reoptimized plan increases the fluence of pencil beams in the right-posterior beam (left side of the image), which traverse the brainstem and deliver low-LET irradiation to the region where target and brainstem overlap.

Base-of-skull chordoma (case 3)

Figure 4 shows a base-of-skull chordoma where the target volume abuts the brainstem. The patient is treated with 2 coplanar beams and a superior oblique beam. Similar to cases 1 and 2, treatment planning based on physical dose alone leads to high LETxD values in the brainstem due to pencil beams incident from the patient's left (right side of the image) that stop in front of the brainstem (Figure 4e). LETxD values can be reduced (Figure 4f) by using pencil beams in the posterior beam that avoid the brainstem laterally (Figure 4b).

Summary of results

Table 1 summarizes the results for LETxD reductions after reoptimization for the brainstem, which is the OAR common to all 5 patients. For all cases, LETxD hot spots exceeding twice the mean target LETxD value were observed in OARs in the reference plan. After reoptimization, LETxD in OARs was reduced to values close to the mean value in the target. DVH comparisons for patients 2–5 are shown in the supplementary materials (Appendix F).

Discussion

Compared to passive scattering and SFUD techniques, IMPT has the potential to improve conformity and reduce the integral normal tissue dose. However, as a consequence of highly modulated fields, IMPT plans may yield highly inhomogeneous LET distributions even for homogeneous physical dose distributions. In particular, IMPT may yield high LET values in serial critical structures within or near the target volume, which exceed the values observed in passive scattering or SFUD. This could lead to an increased complication rate, but this concern is yet to be underpinned by clinical evidence.

We suggest a method based on prioritized optimization that reoptimizes IMPT plans for their LET distribution while limiting degradations of the physical dose distribution. We applied the method to intracranial tumors where the brainstem or optic structures overlap with the target volume. For the cases studied here, high LET values in these structures could be avoided at little cost: degradations to the optimal physical dose distributions were minor. However, in general the method's degree of success depends on patient geometry and beam arrangement (see also case 5 in the supplementary materials, Appendix D, Figure 8). For example, high LET in a critical structure overlapping the target can only be avoided if that structure falls within the entrance region of some pencil beams, i.e. the structure can not only receive dose from Bragg peaks placed at its location. If this is not fulfilled, changing the incident beam directions may be necessary to reduce LET hot spots.

LETxD redistribution beyond OARs

The objective in the above examples was to reduce potential areas of high RBE in OARs. As seen in Figures 1–3, this is mostly achieved by shifting LET hotspots to other regions at the periphery of the target, which may still contain functioning brain tissue. Hence, it is implicitly assumed here that OARs are contoured as to represent structures that are more important to spare than the remaining normal brain. Additional iterations of prioritized optimization can be applied to reduce LETxD in all of the normal brain inside and outside of the PTV, and concentrate high LET exclusively in the GTV. However, these modifications

are typically associated with more substantial degradation of the physical dose distribution. The treatment plan that minimizes the healthy tissue dose in the beam entrance regions preferentially uses Bragg peaks placed at the distal edge of the target, as these pencil beams deposit additional dose for free while traversing the target. Unfortunately, this leads to high LETxD values in the periphery of the GTV, and low values in the center of the GTV (Figures 1,3,4d). In contrast, high LET in the GTV is achieved if as many protons as possible stop within the GTV. In terms of physical dose, this corresponds to an inefficient use of protons, which conflicts with the goal of minimizing healthy tissue dose in the entrance region.

At first glance, it appears plausible to maximize LETxD in the GTV as a means to increase the RBE-weighted dose. However, the alternative strategy is to allow higher physical dose in the GTV. Hence, to assess the potential benefit of LETxD escalation in the GTV, such treatment plans should be compared to what physical dose escalation can achieve. In this context, we point out that higher doses in parts of the GTV can often be achieved without increasing normal tissue dose. This effect is also referred to as the *price of uniformity*, a term that alludes to the mathematical certainty that adding an IMPT optimization objective that penalizes hot spots in the GTV will worsen the combined remaining planning objectives.

To illustrate this, we consider the atypical meningioma case (Figure 1). We apply an additional prioritized optimization step to the treatment plan in Figure 1e/f. The only objective is to maximize the mean physical dose in the GTV. The physical dose constraints are the same as for the plan in Figure 1e/f, except that the penalty for overdosing the GTV has been removed (while keeping the overdose penalty for the part of the PTV that is not GTV). The exact formulation is provided in the supplementary material (Appendix E.1). Figure 5 shows the difference in physical dose between the dose-escalated plan and Figure 1e. By construction, the normal tissue receives approximately the same dose, but much higher doses of up to 100 Gy can be achieved in the center of the GTV. The mean physical GTV dose is increased from 51 Gy to 58 Gy without compromising conformity or increasing integral dose to the healthy tissue. Hence, if dose escalation in the GTV is the goal, physical dose and LETxD should be considered jointly, rather than reoptimizing the LETxD distribution alone while constraining the physical dose.

RBE versus LET based IMPT planning

While this report suggests an IMPT planning method based on LET, other authors have proposed IMPT planning based on RBE-weighted dose [2–5]. Whether LET-guided or RBE-based planning is appropriate depends on the application and the goals of treatment planning. Both methods may coexist. The approach in this paper is motivated by the following scenario:

1. We are concerned about serial OARs with maximum dose constraints that are located within/near the target. We would like to avoid LET hotspots in these OARs as this may increase the risk of complications by an unknown amount.

2. We do not want to lower the physical dose in the target volume compared to current practice. Multiple reasons support this practice, such as skepticism regarding the accuracy of RBE models for the tumor and the necessity to comply with clinical trial protocols that specify the physical prescription dose.
3. While reducing LET hotspots in OARs, we want to assess and control physical dose increases in normal tissues compared to the treatment plan that is optimal in terms of physical dose alone. This is because the tradeoff between the clinical value of LET reduction versus physical dose increase is unknown.

These goals are achieved with the proposed combination of physical dose and LET-guided planning using prioritized optimization. However, in other situations, IMPT optimization based on RBE-weighted dose may be appropriate. For example, if dose escalation in the GTV is the goal, as described above and similarly in [4,5], this can be achieved via objective functions evaluated for RBE-weighted dose.

Potentially, plan improvements can be achieved by lowering the physical dose in the target in areas of high LET, based on the assumption that RBE is larger than 1.1. The reduced target dose may in turn lead to lower doses in the normal tissue. Such treatment plans can be created by evaluating target coverage objectives for RBE-weighted dose rather than physical dose [2,3]. Currently, practitioners are hesitant to pursue this approach as it risks under-dosing the tumor if the RBE is overestimated. However, advances in RBE measurements [17] may facilitate such approaches in the future.

Conclusion

We describe a prioritized optimization method to reoptimize IMPT plans in terms of their LET distributions while limiting the degradation of the best possible physical dose distribution. The method does not depend on tissue or patient-specific RBE, which currently is associated with large uncertainties. It can be applied to patients where serial critical structures are located within or adjacent to the target volume, in order to avoid high LET values in these structures. This makes the use of IMPT safer considering that the risk of side effects associated with high LET is largely unknown.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Summary

High linear energy transfer (LET) values in serial normal tissues located within the target volume may increase the risk of side effects after proton radiotherapy. We present a treatment planning method for intensity-modulated proton therapy based on prioritized optimization, which avoids elevated LET in critical organs. The approach is demonstrated for meningiomas, base-of-skull chordomas and ependymomas where the brainstem, chiasm or optic nerve overlay the target volume.

Figure 1.

Plan comparison for the atypical meningioma (case 1): a) contours for target volume (red), GTV (brown), brainstem (green), optic structures and pituitary gland (yellow); c and e) physical dose and LETxD for the reference plan; d and f) physical dose and LETxD for the reoptimized plan; b) difference in physical dose, positive values indicate higher doses in the reference plan.

(a)

(b)

Figure 2.

DVH comparison for the atypical meningioma (case 1) between reference plan (solid lines) and reoptimized plan (dashed lines). (a) physical dose DVHs, showing identical target coverage for both plans; (b) DVHs evaluated for LETxD (scaled with $c = 0.04 \mu\text{m}/\text{keV}$). In the LETxD DVH of the brainstem, voxels that receive less than 10 Gy physical dose in the reference plan were removed for better visualization. The black lines correspond to all normal tissue voxels in a 1 cm margin around the target volume.

Figure 3.
Plan comparison for the ependymoma (case 2).

Figure 4.
Plan comparison for the base-of-skull chordoma (case 3).

Figure 5.

Difference in physical dose (Gy) between the dose-escalated plan and Figure 1e, i.e. the figure shows the additional physical dose on top of 50 Gy, which can be delivered to the GTV without worsening any normal tissue dose objective. The corresponding LETxD distribution is shown in the supplementary materials (Appendix E.2).

Table 1

LETxD values (scaled with $c = 0.04 \text{ } \mu\text{m/keV}$) in the brainstem for the reference and reoptimized plans. We report the maximum LETxD value in the brainstem as well as the LETxD value that is exceeded in 0.1 cc and 0.5 cc. For comparison, L_d^{ref} and the mean LETxD value in the target are reported.

	case #	1	2	3	4	5
	Tumor	meningioma	ependymoma	chordoma	chordoma	ependymoma
	Volume [cc]	92	69	51	62	53
	Beam directions	3 (2 copl.)	3 coplanar	3 (2 copl.)	6 coplanar	3 coplanar
Reference	LETxD max [Gy]	12.0	11.5	14.8	13.4	13.1
Plan	LETxD 0.1 cc [Gy]	11.2	10.3	13.0	10.2	11.6
	LETxD 0.5 cc [Gy]	9.9	9.2	10.6	7.7	9.3
	L_d^{ref} [Gy]	3.8	3.1	5.0	4.4	3.5
	mean PTV LETxD [Gy]	5.8	5.0	7.1	6.8	5.2
Reoptimized	LETxD max [Gy]	7.4	8.5	8.5	8.9	8.7
Plan	LETxD 0.1 cc [Gy]	5.9	6.7	6.9	6.5	6.6
	LETxD 0.5 cc [Gy]	5.2	5.4	6.2	5.3	5.6