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Variations in linear energy transfer within clinical proton therapy fields and the potential for biological treatment planning

Clemens Grassberger, M.Sc.^{1,2}, Alexei Trofimov, Ph.D.¹, Anthony Lomax, Ph.D.², and Harald Paganetti, Ph.D.¹

¹ Department of Radiation Oncology, Massachusetts General Hospital & Harvard Medical School

² Center for Proton Radiotherapy, Paul Scherrer Institute, 5232 Villigen-PSI, Switzerland

Abstract

Purpose—To calculate the Linear Energy Transfer (LET) distributions in patients undergoing proton therapy. These distributions can be used to identify areas of elevated or diminished biological effect. The location of such areas might be influenced in intensity-modulated proton therapy (IMPT) optimization.

Methods and Materials—Since Monte Carlo studies to investigate the LET distribution in patients have not been undertaken so far, the code is first validated with simulations in water. The code was used in five patients, for each of them three different planning and delivery techniques were simulated: passive scattering, 3D modulation IMPT (3D-IMPT) and Distal Edge Tracking IMPT (DET-IMPT).

Results—The inclusion of secondary particles leads to significant differences compared to analytical techniques. In addition, passive scattering and 3D-IMPT lead to largely comparable LET distributions, while the DET-IMPT plans result in considerably increased LET values in normal tissues and critical structures. In the brainstem, dose-averaged LET values exceeding 5 keV/μm are observed in areas with significant dose (>70% of prescribed dose). In non-critical normal tissues even values >8 keV/μm occur.

Conclusion—This work demonstrates that active scanning offers the possibility to influence the distribution of dose-averaged LET (i.e. the biological effect) without significantly altering the distribution of physical dose. Based on this finding, we propose a method to deliberately alter the LET distribution of a treatment plan in such a manner that the LET is maximized within certain target areas and minimized in normal tissues, while maintaining the prescribed target dose and dose constraints for organs at risk.

Keywords

protons; Monte Carlo; linear energy transfer (LET); relative biological effectiveness (RBE); IMPT

Corresponding author: Clemens Grassberger, Massachusetts General Hospital, Francis H Burr Proton Therapy Center, Boston, MA 02114, Phone +1-617-999-7772, Fax +1-617-724-0368, cgrassberger@partners.org.

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Introduction

The majority of clinical data in radiation therapy is based on treatments with photon beams. Furthermore, prescription doses to cancerous tissue as well as dose constraints to organs at risk are based on clinical experience and not necessarily on direct radiobiological considerations. Consequently, the gold standard, when it comes to characterizing biological effects, is low-LET (linear energy transfer) radiation, i.e. photons. Doses prescribed relative to photon beams lead to the necessity of applying the concept of relative biological effectiveness (RBE) for proton therapy and other particle-based treatments (1).

Proton beam therapy has been based mainly on a generic RBE of 1.1 (1,2). However, it is well known that a single, generic RBE value in proton therapy is only an approximation as the RBE depends on dose (3), endpoint (4), track structure (5), LET (6) and other factors (7).

Even though radiobiologists have been aware of these variations in the biological effectiveness of protons for a long time, these differences were considered too small to be significant clinically. With improved treatment delivery techniques and powerful computational methods available, recent publications have sparked interest in these variations yet again (8,9,10). The ICRU report on proton therapy (7) also emphasizes the sharp relative increments in the RBE on the distal edge and the therefore increased effective range.

Currently, due to lack of biological input parameters, our ability to predict RBE for all tissues in treatment planning is very limited and thus the continuous use of a generic RBE was recommended (7). Even though there are uncertainties, there is one area where the RBE is certainly higher than 1.1: in the area distal to the Bragg peak (11). In this part of the depth-dose curve the average proton energy decreases rapidly leading to an increased LET.

The clinical consequence of this uncertainty at the distal edge of the Bragg peak is the avoidance of beam angles that place the distal edge close to critical structures, excluding possibly advantageous beam arrangements and therefore partially neutralizing the dosimetric advantage of protons. Clarification of the uncertainties at the distal edge, regarding both RBE as well as range, would free up beam arrangements and give more freedom to treatment planners.

The basis of this study is the LET dependency of the RBE. Although the RBE-LET relationship depends on tissue type, endpoint and dose, one can assume that the biological effectiveness increases with increasing LET. While it is true that at very high LET values the RBE decreases again due to overkill effects, this is certainly not the case in the LET range of protons at relevant doses.

In the target area the dose is typically delivered homogeneously. This however does not guarantee a homogeneous distribution of LET values. It is well known that the increase in LET at the end of range, i.e. at the Bragg peak and beyond, is more pronounced in pristine Bragg curves than in SOBPs (12). The LET distribution in an SOBP is diluted because of the contribution of dose from both peaks and the plateau region resulting in a wide range of proton energies. Furthermore, there could be additional dilution in the patient because of frequent interfaces between different materials in the beam path and significant scatter in bone. Tissues with high-Z values (e.g., bone) as well as the application of multiple fields might cause a complex distribution of high LET areas, not necessarily limited to the edge of the target. Thus, one of the reasons why clinical data may indicate that a generic RBE of 1.1 is acceptable might be that the LET distribution in the patient is lower than expected from experiments or calculations in homogeneous media.

LET distributions in a patient geometry have so far only been calculated with analytical methods (8,10) or using interpolations based on Monte Carlo calculations in homogeneous media (9). Our work is the first calculating LET directly using Monte Carlo particle tracking in a patient CT geometry, taking into account secondary particle production. Monte Carlo simulations are widely regarded to be the most accurate method to estimate the effects of radiation (7,13).

The purpose of this work was to analyze the three-dimensional distribution of dose-averaged LET values in five different proton therapy patients in order to

- simulate the distribution of LET values in proton therapy patient fields using the most accurate Monte Carlo method
- estimate the portion of the volume within a given structure that is subject to elevated LET values
- compare the LET distributions for passive scattering and different active scanning techniques
- demonstrate how different scanning approaches, whilst achieving similar physical dose distributions, can have quite different LET distributions leading to a potential for biologically motivated treatment plan optimization

Methods and Materials

LET calculations

All calculations were done using the Geant4 code (14) considering all relevant particles (primary and secondary protons, electron, photons). The physics setting is described elsewhere (15).

For the simulations of the passive scattering treatments, the code was used to simulate the whole treatment head setup (16) including aperture and range compensator, and the patient geometry based on the CT information (17). For IMPT on the other hand the possibility to use measured beam parameters for beam characterization allowed us to “create” the particles in front of the patient geometry.

Beam and patient information were transferred directly from the planning system (XiO, Computerized Medical Systems Inc.) to the Monte Carlo code previously described for passive scattering (18). In the case of IMPT, the research version of *KonRad* (19) was used to generate the treatment plans, which were then directly converted to an input suitable for the Monte Carlo simulations.

The dose-averaged LET (LET_d) distributions were generated by scoring each energy deposition event on the patient's CT grid. At each energy deposition associated with a particle's energy loss (dE), the length of the particle step (dx) was obtained (by subtracting the post-step from pre-step position in space). All values were scored voxel by voxel (v) and as dose-to-tissue in order to calculate the LET_d in MeV/g cm²:

$$LET_d(v) = \frac{\sum_{events} dE \cdot (dE/dx)_p^{\frac{1}{2}}}{\sum_{events} dE} \quad (1)$$

The dose and LET_d distributions are simulated for each treatment field separately, from which the LET_d distribution for all fields F , each delivering the dose D_F , was then obtained through

$$LET_d(v) = \frac{\sum_F LET_d^F(v) \times D_F(v)}{\sum_F D_F(v)}. \quad (2)$$

When simulating LET_d using Monte Carlo simulations, the cut-off defined to stop further tracking of the proton can have a significant influence (20). We tracked all particles down to zero kinetic energy (except for the photons which have a cut-off of 50 keV). The production threshold for secondary particle tracking was set to 0.05 mm.

In this study, the dose-averaged LET is used, meaning that the LET is averaged in such a way that the contribution of each particle is weighted by the dose it deposits. We thus assume that the dose-averaged LET is a surrogate for biological significance of high-LET areas. However, while for proton beams the number of particle tracks crossing a sub-cellular structure is quite large (21), one has to keep in mind that for high-LET ion beams the number of tracks per sub-cellular target may be considerably smaller, resulting in an inhomogeneous local dose distribution. In this case, the track averaged LET might become more meaningful. This illustrates the limitations of the LET concept because at low energies (and therefore low fluence for a given dose), the track structure becomes increasingly important (5). A discussion on these issues is beyond the scope of this paper.

Proton delivery methods

Most proton therapy patients are treated with passive scattered delivery. Passive scattering results in broader energy distributions due to scattering in the beam path. Thus, it is expected that SOBP fields show a less pronounced increase in LET at the end of range than pristine Bragg peak fields. Analyzing single fields with various ranges in different patients, we confirmed that the high-LET areas are around 8–12 keV/μm for pristine peaks (depending on beam energy), while always ≈8 keV/μm for passive scattering SOBP fields.

Proton beam scanning allows the delivery of intensity-modulated fields (IMPT). Lomax (22) described four different methods of intensity modulation for protons: 2D, 2.5D, DET and 3D. Two of these methods, 3D modulation IMPT (3D-IMPT) and Distal Edge Tracking IMPT (DET-IMPT) cover the spectrum of possible solutions for IMPT. In DET-IMPT the optimization routine assigns weights only to the distal beam spots, reducing the number of spots delivered per field, whereas for 3D-IMPT, Bragg peaks are selected that cover the whole target volume. The fields in the 3D- and DET-IMPT plans were set to the same angles for all simulated patients.

Except for some hotspots at the end of range, which are significantly reduced by using multiple fields, we have found that the LET_d distributions for passive scattering and 3D-IMPT are largely similar. We therefore decided to present only the comparison between 3D-IMPT and DET-IMPT, since here the comparison between almost identical dose distributions but vastly different LET_d distributions is most striking.

The differences regarding robustness to calculation errors, inter-fraction and inter-field motion between the two IMPT techniques have been examined in detail by Lomax (23,24), concluding that 3D-IMPT is far more robust than DET-IMPT. Another disadvantage of

DET-IMPT is a lower homogeneity inside the target, especially if the target is large. To the authors knowledge DET-IMPT is not employed clinically.

We want to emphasize that the aim of this study is *not* to compare these different IMPT treatment modalities, but to exploit the fundamentally different spot weighting of these two techniques in order to study the differences in LET distributions that may arise from different planning approaches.

Validation of the code

Since Monte Carlo studies to investigate the LET distribution in patients have not been undertaken so far, our code was first validated by comparing simulations in a water phantom to published data. The data agrees well with previous studies (20), apart from deviations arising from the inclusion of secondary particles. These include a higher LET_d in the entrance region caused by secondary protons (≈ 0.8 keV/ μ m instead of ≈ 0.5 for primary protons only), a lower LET_d peak and a “tail”, both due to photons. In our simulations primary and secondary protons, electrons and photons were tracked. We confirmed that these particles contribute >99% of the deposited energy in areas with significant absolute dose (>1% of prescribed dose). Note that other particles, e.g. neutrons, would have to be included if long-term side effects due to neutron background in proton therapy would be considered in the treatment planning process.

Results

Five patients were selected for this study, four head and neck cases and one prostate case. For each of them, both 3D-IMPT and DET-IMPT plans were calculated. The results depend on the beam ranges and the exact field arrangements and the data presented here focuses on these three representative cases:

- Patient I: a deep seated chordoma, treated with multiple fields with a large angular separation
- Patient II: a superficial neoplasm, treated with multiple fields with a small angular separation
- Patient III: a prostate case, involving higher proton energies, and using two parallel opposed fields

Patient I – pediatric chordoma

The first case is a pediatric chordoma located at the clivus, extending into the right hemisphere. The tumor was originally treated to 59.4 Gy(RBE) using conformal proton therapy with fields coming from 3 different angles: 2 coplanar fields entering from 80 and 260 degrees, and a 3rd non-coplanar field entering the skull through the frontal lobe (to help visualize this complex beam setup, a movie is available at www.redjournal.org). The treatment plan for this patient was driven by many factors, since there are various radiosensitive structures very close to the target. The chiasm, both optical nerves, the left cochlea, the pituitary gland and the brainstem all received doses close to their respective maximum dose constraints (e.g. 60 Gy(RBE) for chiasm and pituitary).

The dose and LET_d distributions of a representative slice in the 3D-IMPT plan are shown in the upper part of Fig. 1. There is a spread-out region of intermediate LET_d of around 3–4 keV/ μ m covering the whole gross tumor volume (GTV) and the area posterior to it. LET_d hotspots reaching values above 4 keV/ μ m can be seen posterior to the GTV and close to the zygomatic bone. The hotspot close to the zygomatic bone is presumably caused by a

combination of very shallow beam spots (with less range-straggling and therefore high LET_d) and increased secondary particle production in the bone.

The lower part of Fig. 1 visualizes the dose and LET_d distributions of the same slice in the DET-IMPT plan. The quality of the plan is not significantly different, i.e. both 3D- and DET-IMPT meet the dose constraints. The main differences are far lower LET_d values in the GTV with an average around 2 keV/ μ m and hotspots above 5 keV/ μ m posterior to the target and in the center, where brainstem and pituitary gland are located.

The differences become much more apparent in the LET-Volume-Histograms (LVHs). Figure 2 (upper left) shows the data for the GTV where the LET_d is considerably enhanced all over the target. The brainstem (upper right) and pituitary gland (lower left) show a different picture, suggesting that the DET-IMPT plan creates LET_d -hotspots (defined as values exceeding 4 keV/ μ m). This is also shown graphically in the lower right picture, where the difference [LET_d (3D-IMPT) – LET_d (DET-IMPT)] is plotted.

Patient II – superficial benign neoplasm

The second case is a benign neoplasm mainly located in the frontal lobe just beneath the frontal bone, but extending all the way through the frontal, down to the ethmoid sinuses. The tumor was treated using a frontal and two lateral fields entering through the left and right frontal lobes. The design of this plan was driven by the requirement to spare the retina, all other critical structures (optical nerves, pituitary gland, brainstem) were far below their constraints.

The dose and LET_d distributions of a representative slice of the two IMPT plans can be seen in Fig. 3. The 3D-IMPT plan leads again to higher values in the GTV and a lower LET_d in the region around the retinas. The DET-IMPT plan features lower values in the GTV and areas with very high LET_d (>9 keV/ μ m) outside the target volume. These observations are confirmed by the LVHs in Fig. 4. In the right retina the DET-IMPT technique leads to hotspots, while in the chiasm shown on the right both plans produce LET_d values in excess of 9 keV/ μ m.

The main difference compared to patient I is that the observed LET_d distributions generally show higher values. This is caused by the fact that all three fields enter from similar directions. Therefore peaks at the end of range are not diluted by fields entering from the opposite direction.

Patient III – prostate

Our third case is a prostate patient, irradiated by two opposing fields passing through the femoral heads in transit to the target. Figure 5 visualizes the LET_d distributions for 3D-IMPT (left) and DET-IMPT (right).

The values are generally far lower than in the other two patients. This is due to the high initial beam energy (up to 190 MeV) and the larger amount of range-straggling which leads to lower LET_d -peaks at the end of range. However even in these “diluted” LET_d distributions, the difference between 3D-IMPT and DET-IMPT is clearly visible in the CTV.

The dose distributions for this patient (not shown here) are not comparable. Because of the large target size and only two considered fields, the DET-IMPT plan is not able to cover the target homogeneously. Additionally, DET would cause concern regarding inter-fraction motion. The results are instructive nevertheless, since it is shown that increased range-

straggling present in the treatment of deep-seated tumors lowers the LET_d -variations considerably.

Discussion

In all patients, 3D-IMPT leads to higher LET_d values in the tumor and less pronounced hotspots in normal tissues compared to DET-IMPT. The dose distributions for the two techniques are clinically equivalent for patient I and II.

The enhanced hotspots in the DET-IMPT plans result from the different weighting of beam spots: the DET-IMPT plans can only assign weight to the distal edge, hence the LET_d values are increased there compared to the 3D-IMPT plan, which deposits Bragg peaks throughout the target volume. This also leads to the observation that 3D-IMPT plans produce higher LET_d -values in the target. The lower left picture in Fig. 2 visualizes the difference between the two techniques graphically for patient I: the quantity plotted is $[LET_d(3D-IMPT) - LET_d(DET-IMPT)]$. The differences in the target and the brainstem are up to 3 keV/ μ m.

Furthermore, our analysis shows that the LET_d can vary by up to a factor of 2 in the target and by more than a factor of 3 in adjacent critical structures. Unfortunately, LET_d values cannot be translated into RBE values without significant uncertainties in particular for *in-vivo* endpoints.

In-vitro experiments with V79 cells demonstrated a RBE >2.0 for LET values of >7.7 keV/ μ m (25). However, the survival curve associated with the V79 cell line has a large shoulder and is thus not representative for most tissues encountered in humans. However, the LET values found in this study suggest that the deviation from a generic RBE of 1.1 could be significant even for human tissues *in-vivo*.

The LET is one of several factors influencing the RBE of protons (the others being dose, fractionation, tissue, and biological endpoint) but it is also a parameter whose distribution could potentially be influenced at the time of planning. While it might be difficult to incorporate all parameters influencing RBE, e.g. α/β -ratio, dose, fractionation etc., biologically motivated treatment planning could at least be guided by LET. For instance, although we experience almost the entire LET spectrum when analyzing LET distributions in a clinical heavy ion beam, significant contributions to dose in proton beams are entirely in the region where the RBE only increases with LET. Thus, it might be feasible to incorporate physics-related RBE effects using a single physics parameter, the LET.

The most important finding of this study is that the distribution of LET_d may vary when comparing two clinically equivalent dose distributions based on two different treatment plans or treatment delivery concepts. The basis for this is the fact that dose can be interpreted as particle fluence times LET and thus equivalent doses can be delivered with low numbers of higher LET particles or high numbers of lower LET particles (26). Consequently, the LET_d distribution can be deliberately altered by pre-selection of beam spots before the optimization process. In order to use the LET_d information in biologically motivated treatment planning for (intensity-modulated) proton therapy, the following procedure might be applied for each row of beam spots:

- if a critical structure is located distal to target, select all points for optimization. This leads to a reduction of the weight that is put on the deepest beam spot, which is located just before the critical structure, and reduces the LET_d there.
- if a critical structure is located proximal to target, select only the distal half of the points for optimization. This reduces the LET_d in proximal structures without pushing high LET_d values into the distal structures.

- For cases where lateral fields are available, the fall-off towards critical structures could be taken over primarily by lateral edges, which would further lower the LET_d there. Effects of range degradation, i.e. degrading the dose fall-off towards the critical structure, need to be considered though.

Figure 6 schematically shows which beam spots would be available to the optimization routine for two opposing fields and which points a lateral field III would take over from their distal edges. This pre-selection of beam spots could be incorporated into an inverse-planning IMPT-optimization to yield a superior biological dose distribution.

The reasons for these simple selection criteria arise directly from the different weighting mechanisms of 3D-IMPT and DET-IMPT and the LET_d profile of a pristine peak. Furthermore, the avoidance of selecting only the most distal beam spot presumably leads to plans that are more homogeneous and more robust with respect to inter-fraction and inter-field motion, as compared to DET-IMPT plans.

The ability to influence high LET_d areas within the target volume, which we have demonstrated, could also have potential implications for delivering inhomogeneous tumor dose distributions, e.g. to place high LET_d volumes in hypoxic tissues.

A note of caution: While the concept of LET might be convenient and is used in this work, one has to keep in mind that characterizing a biological effect at a given dose and for a given tissue endpoint by using a single parameter, i.e. LET, is misleading. The LET is a macroscopic parameter and in order to parameterize physics on a cellular level it is only a crude approximation, as track structure and micro- or even nano-dosimetry play a role.

Conclusions

LET distributions in the patient have previously been calculated using analytical methods (8) or by interpolation from data obtained in water phantoms (9). However, our study is the first to simulate the LET_d distribution directly in the patient using Monte Carlo and taking into account secondary particle production. The main findings are that

- secondary particles do have a significant influence on the LET_d distribution.
- single IMPT fields lead to LET_d values of 8–12 keV/ μ m (depending on range), while in passively scattered fields the highest LET_d values observed are $\approx$ 8 keV/ μ m.
- in IMPT treatment plans, LET_d values within the target range from $\approx$ 1.5–4 keV/ μ m, but this is highly dependent on the optimization technique used.
- elevated LET_d values (>10 keV/ μ m) are present in the distal fall-off of proton fields but are not significant in the entrance region.
- LET_d values exceeding 5 keV/ μ m occur in critical structures in areas of significant dose ($>70\%$ of prescribed dose), values exceeding 8 keV/ μ m are also observed, although generally only in areas with low dose.
- the optimization technique has a significant influence on the LET_d distribution.
- deep-seated targets show considerably lower LET_d due to range-straggling.

Our results might have implications in optimizing treatment plans. While the possibilities of influencing the areas of elevated LET values is quite limited in broad-beam proton therapy, beam scanning in conjunction with intensity-modulated proton therapy might allow the planner to influence the LET distribution by pushing elevated LET values away from critical structures without altering the dose distribution.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Representative slice of the 3D-IMPT (upper part) and DET-IMPT (lower part) plans for patient I, calculated with Monte Carlo. Contours for GTV and brainstem are shown in blue and green, respectively. Left: dose in percent of prescribed dose, entrance direction of the two co-planar fields indicated by white arrows. Right: LET_d distribution in keV/ μ m. Dose and LET_d values below 0.1% of maximum values have been made transparent.

Fig. 2. LET_d -volume histograms (LVHs) of GTV, brainstem and pituitary gland for patient I. The figure at the lower right visualizes the differences between the LET_d distributions, i.e. [LET_d (3D-IMPT) - LET_d (DET-IMPT)]. The red areas indicate that the 3D modulation plan has higher LET_d values, while the blue areas shows that the DET-IMPT plan causes a higher LET_d . The scale plots the difference in LET_d in keV/μm.

Fig. 3. Representative slice of the 3D-IMPT (upper part) and DET-IMPT (lower part) plans for patient II. Left: dose in percent of prescribed dose. Right: LET_d distribution in keV/ μ m. Dose and LET_d values below 0.1% of maximum values have been made transparent. Contours for GTV, retinas and chiasm are shown in red, green and yellow, respectively.

Fig. 4.
LVHs of GTV, right retina and chiasm for patient II.

Fig. 5. Representative slice showing the LET_d distribution of the 3D-IMPT (left) and DET-IMPT (right) plan for patient III (color bar in units of keV/μm). Values below 0.1% of maximum have been made transparent. The target is contoured in white, entrance direction of beams indicated by white arrows.

Fig. 6. Schematic illustration to show which beam spots would be available to the optimization routine for two opposing fields and one lateral field in the presence of two critical structures left and right of the target.