Clinical evidence of variable proton biological effectiveness in pediatric patients treated for ependymoma

Christopher R. Peeler a,b, Dragan Mirkovic a, Uwe Titt a, Pierre Blanchard c,d, Jillian R. Gunther c, Anita Mahajan e, Radhe Mohan a, David R. Grosshans c,e,⇑

a Department of Radiation Physics, The University of Texas MD Anderson Cancer Center, Houston; b Department of Radiation Oncology, Villejuif, France; c, d Gustave Roussy, Université Paris-Saclay, Department of Radiation Oncology, Villejuif, France

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Background and purpose: A constant relative biological effectiveness (RBE) is used for clinical proton therapy; however, experimental evidence indicates that RBE can vary. We analyzed pediatric ependymoma patients who received proton therapy to determine if areas of normal tissue damage indicated by post-treatment image changes were associated with increased biological dose effectiveness.

Material and methods: Fourteen of 34 children showed T2-FLAIR hyperintensity on post-treatment magnetic resonance (MR) images. We delineated regions of treatment-related change and calculated dose and linear energy transfer (LET) distributions with Monte Carlo. Voxel-level image change data were fit to a generalized linear model incorporating dose and LET. Cross-validation was used to determine model parameters and for receiver operating characteristic curve analysis. Tolerance dose (TD50; dose at which 50% of patients would experience toxicity) was interpolated from the model.

Results: Image changes showed dependence on increasing LET and dose. TD50 decreased with increasing LET, indicating an increase in biological dose effectiveness. The cross-validated area under the curve for the model was 0.91 (95% confidence interval 0.88–0.94).

Conclusions: Our correlation of changes on MR images after proton therapy with increased LET constitutes the first clinical evidence of variable proton biological effectiveness.

⇑Corresponding author at: Proton Therapy Center, The University of Texas MD Anderson Cancer Center, 1840 Old Spanish Trail, Unit 1150, Houston, TX 77054, United States.
E-mail address: dgrossha@mdanderson.org (D.R. Grosshans).

1 These authors contributed equally to this work.

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Given its potential to better spare normal tissue than photon-based radiotherapy, proton therapy is increasingly used to treat numerous cancer types. This advantage is inherent to the physical properties of charged-particle dose deposition called the Bragg curve, with low-dose in the entrance region, increasing to peak dose (called the Bragg peak) near the end of the range, followed by an abrupt stop. Such properties are thought to be of special benefit for pediatric patients requiring radiotherapy for brain tumors, where low-dose radiation exposure, unavoidable even with advanced photon techniques, may result in significant radiation-induced adverse effects such as cognitive decline [1,2].

In current clinical practice, protons are considered to be uniformly 10% more biologically effective than photons. The ratio between proton and photon doses for an equivalent biological effect is termed relative biological effectiveness (RBE), and the physical dose for proton therapy is obtained by dividing the photon dose by 1.1. However, increasing evidence suggests that the biological effectiveness varies along the path of a proton beam. Increases in linear energy transfer (LET) with slowing of protons as a function of depth is one of the main determinants of proton biological effectiveness [3]. For photon therapy, in contrast, the LET is essentially constant. Past experiments have shown that proton RBE increases modestly with LET in a mostly linear fashion [4]. Based on these studies, many models of proton RBE as a function of dose, LET, and α and β values have been created by using subsets or even all of the available experimental data [3.5–11]. The models have invariably relied on dose-averaged LET (LETd). Newer studies suggest a non-linear relationship of RBE and LET as well as potentially higher biological effectiveness, especially in the region from just before to beyond the Bragg peak, bringing the validity of the developed models into question [12].

Although laboratory studies suggest that biological effectiveness increases near the end of the proton beam range, to date little is known of whether such changes are important clinically. Initial studies seeking clinical evidence of increased biologic effectiveness...
have had mixed results [4], perhaps because such studies have sought to map proton RBE as a function of dose and LET (and sometimes other factors) using models based on in vitro experiments with cancer cell lines [4,5,12–14]. Such models, which typically assess clonogenic survival, may not be applicable to complex in vivo processes that involve multiple cell types, such as radiation-induced brain damage.

In the realm of photon therapy, the appropriate safe and effective doses for treating various types of tumors and the tolerance doses for normal tissues have been derived from analyses of decades of data on patient outcomes [15–18]. When assessing a newer technology such as proton therapy, it would make sense to take a similar approach to develop such knowledge. However, because of the limited availability of proton therapy, patient data are limited, yet the high cost of proton therapy facilities produces pressure to fully elucidate the benefit of proton therapy [19–21].

Our group recently identified that, in comparison to patients treated with photon therapy, children with ependymoma treated with protons more often developed changes in normal brain parenchyma on MR images after treatment [22]. Although image changes do not always indicate permanent adverse neurological defects [22–25], they are still considered a grade 1 response according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 [26] grading scale and may be a harbinger of more severe reactions [27,28]. Imaging changes such as these are thought to reflect early tissue damage [25] and thus are important for studying the biological properties of protons as a function of dose and LET. Such image biomarkers are potentially more likely to detect subtle changes due to differences in RBE that may be difficult to detect clinically. We sought to analyze patients treated with protons to determine if the location of changes on post-treatment images was related to physical proton characteristics, more specifically LET. By looking at voxel-level data rather than only volume-based data, we sought to improve our ability to correlate clinical imaging data with radiation dose and LET.

Methods

Patient cohort and image processing

We analyzed 34 pediatric patients with ependymoma treated with proton therapy; all were participants in a prospective protocol to assess normal tissue toxicity with proton therapy. All were treated with passive scatter proton therapy. Demographic and clinical information for all patients is presented in Table 1. A subset of 14 patients exhibited post-treatment changes on MR images, observable as T2-FLAIR hyperintensity with or without enhancement on T1 post-contrast sequences. Those MR images were rigidly registered with treatment planning CT images by using an Eclipse treatment planning system v9.0 (Varian Medical Systems, Inc., Palo Alto, CA). Regions of treatment-related change in normal brain parenchyma were contoured by a practicing radiation oncologist at the variable MC\textsuperscript{2}, based on MCNPX [29], was used to recalculate treatment plans to obtain dose and LET distributions. The MC\textsuperscript{2} system has been described and validated elsewhere [30,31]. The MCNPX simulation provided dose and total fluence (the number of protons traversing an area) in each voxel, which were used to calculate the track-averaged LET (LET\textsubscript{T}). [32]. Although most studies have been based on dose-averaged LET (LET\textsubscript{d}), the LET\textsubscript{T} is an acceptable approximation for LET\textsubscript{d} for lower values of LET, such as those encountered in most treatment plans, because LET\textsubscript{T} is linearly proportional to LET\textsubscript{d} in this low-LET region [33]. Many of the treatment plans consisted of a primary plan and 1 or 2 boost plans. As such, the dose and LET values used are sum and average values, respectively, over all plans for a given patient.

Voxel-level analysis of image changes

To avoid subdividing the dataset, all image changes were evaluated as being within the contoured whole brain structure, including those changes occurring within the brainstem. The contoured image change regions were identified with voxels represented as binary response (image change) 1 whereas voxels within the brain outside the response region were represented as response 0. Voxel data points with dose <1 Gy were removed from the dataset because these points were effectively noise and no image change was expected. The Matlab 2014b (The MathWorks, Inc., Natick, MA) glmfit function was then used for a generalized linear model fit of the data according to the binomial distribution with a probit link function. Dose and LET were taken to be the predictors in the model. The probit model assumed in the fitting is the normalized cumulative distribution function. Assuming mean $\mu = 0$ and the standard deviation $\sigma = 1$ results in the following equation

$$P = F(\phi) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\phi} e^{-\frac{c^2}{2}} dc$$

which is the same basic probit model used in the Lyman model for normal tissue complication probability [34]. In this case $P$ is the probability of image change. The result of the fitting is a set of coefficients for a linear function of dose and LET, which is represented by the variable $c$ in Eq. (1).

Statistical analysis

A set of six clinical and treatment factors were selected for logistic regression analysis to identify any associations with the presence of image changes. Of the clinical factors analyzed by Gunther et al., age at radiotherapy and time before radiotherapy (after surgery) were selected for inclusion in this analysis because of their trends toward significance in that study [22]. The other four factors selected for this study were mean and maximum LET and mean and maximum physical dose within the clinical target volume (CTV). Univariate and multivariate logistic regression analyses were done with Matlab 2014b to identify any significant associations with the presence of image changes. Odds ratios and 95% confidence intervals (CI) were calculated for each factor. Factors with $P$ values <0.25 on univariate analysis were included in the multivariate analysis. No interaction variables were included in the multivariate analysis. A form of leave-one-out cross validation was used to test the robustness of the fitted generalized linear model. Cross validation was done by successively leaving out all of the voxels (both response and non-response) from each individual patient with image changes and then testing the model on the left-out set of voxels (i.e., the left out patient). Data from patients without image changes were included in all training datasets and effectively served as additional control data for no image change. Model parameters were calculated for each of the 14 “left-out” patients. For each iteration, a receiver operating characteristic (ROC) curve

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was produced and the area under the curve (AUC) was calculated with the Matlab perfcurve function.

Results

Six clinical and treatment factors (Table 2) were analyzed for potential associations with the presence of image changes. Of these factors, only maximum LET in the CTV was found to be significant \( (P = 0.02) \) on univariate logistic regression analysis.

\[ P \text{ values for mean LET in the CTV} \ (P = 0.06), \text{age at radiotherapy} \ (P = 0.22), \text{and time before radiotherapy} \ (P = 0.09) \text{were all less than 0.25 and were thus included in multivariable logistic regression analysis. None of these factors were subsequently found to be significant on multivariable analysis.} \]

\[ A \text{ generalized linear model for image change based on dose and LET predictors was produced. The generalized linear model is represented by the following equation} \]

\[ c = 1.2 + \text{LET}_i + 0.14 \times \text{Dose} - 11.2 \]

in which the coefficients are the mean values determined through cross-validation. The standard deviations of the \( \text{LET}_i \) coefficient, and time before radiotherapy \( (P = 0.09) \) were all less than 0.25 and were thus included in multivariable logistic regression analysis. None of these factors were subsequently found to be significant on multivariable analysis.}

\[ \text{Abbreviations: Bl} = \text{bilateral}, \text{GTR} = \text{gross total resection}, \text{Infra.} = \text{infratentorial}, \text{Lt} = \text{left}, \text{STR} = \text{subtotal resection}, \text{Supra.} = \text{supratentorial}, \text{RT} = \text{radiotherapy}, \text{WM} = \text{white matter.} \]
dose coefficient, and intercept were 0.1, 0.01, and 0.7 respectively. Cross-validation of the model generated 14 ROC curves, one for each leave-out iteration. The cross-validated AUC for the model was 0.91 with a 95% confidence interval of 0.88–0.94.

To visualize the relationship between image change, dose, and LET for different values of dose and LET, Fig. 2A and B display two-dimensional representations of the model for constant LET of 1, 3, and 5 keV·μm⁻¹/C₀ and (B) constant physical dose of 30, 50, and 70 Gy. A three-dimensional representation of the model is included in Appendix A in Fig. S1. The model was evaluated for a distribution of dose and LET values to produce the surface plot. The more traditional TD₅₀, the tolerance dose at which a toxic effect would be expected in 50% of patients (in this case voxels), for different values of proton LET, is presented in Fig. 3. The TD₅₀ data were fit with a linear equation (the expected result from the generalized linear model fitting), which is represented by Eq. (3).

$$TD_{50} = 80.0 - 8.57 \times LET$$  \hspace{1cm} (3)

TD₅₀ clearly decreases with increasing LET, which indicates an increase in the biological effectiveness of proton dose with increasing LET.

A qualitative representation of the model is presented in Fig. 4 for an example case. Dose and LET distributions for the representative patient are plotted on an axial CT slice in Fig. 4A and B. The probability of image change is plotted in Fig. 4C. Areas of increased probability of image change predicted by the model (yellow and red areas of the colorwash, panel C) can be seen to overlap with the region of image change indicated by the contour generated from the registered post-treatment MR image (red outline, panel C).

**Discussion**

Variations in the biological effectiveness over the range of a proton beam are not currently incorporated into clinical treatment planning. This is primarily because of uncertainties in published RBE values and the lack of clinical evidence that the use of a constant RBE value leads to suboptimal outcomes [4]. Here we addressed the latter, providing evidence that post-treatment imaging changes are associated not only with radiation dose but also with LET. In pediatric patients with ependymoma treated with proton therapy, we found that the dose at which image changes occurred was lower when combined with elevated LET values, indicating an increase in biological dose effectiveness with increased LET. The analysis was done with a novel method that incorporates voxel-level data to correlate imaging change with physical dose and LET data from the radiation treatment plan. This is highly significant given concerns regarding increased rates of normal tissue injury in pediatric patients treated with proton therapy. Being able to predict and potentially prevent toxicities would ultimately improve radiation treatment design and outcomes. The methods developed may also be applicable to other patient datasets disease types.

We chose the probit form of the model primarily because many previous dose–response studies in radiation oncology have used the Lyman normal tissue complication probability computation model, which is a probit model [34]. Because the published Lyman model does not have an LET component, it was not appropriate for
use here in its standard form. We were, however, able to extract a TD50 parameter because our model is based on the probit function, which facilitates comparison of results with the more traditional models and analyses. Published values for TD50 of necrosis/infarction in the brain (the most closely related normal tissue effect for which large amounts of data are reported) for photons are in the range of 60–75 Gy [15,34–36]. Our own analysis indicates that, for this set of patients, the TD50 for voxel image change spans a similar range for typical low proton LET values of 0–2 keV μm⁻¹. Such low LET values are common in the entrance region and portions of the target volume and have a similar biological effect as photons [4]. Higher LET protons corresponded to lower TD50 values, which in turn correspond to greater biological effectiveness. Here these LET values are in line with those near the end of the range. Assuming a TD50 of 65 Gy for brain necrosis for photons, the ratio of the photon values to that of protons eventually exceeds 1.1, which is the currently assumed value for proton RBE for clinical purposes. Notably, no definitive TD50 has been reported for image changes in photon radiotherapy, yet these changes do represent early tissue damage [25].

As was true in the study from Gunther et al. [22], the clinical factors age at radiotherapy and time before radiotherapy approached significance on univariate analysis in our study but were not significant on multivariable analysis. Unfortunately, these clinical factors cannot be overcome by the use of the voxel-level analysis since they are patient specific and thus modeling their effects depends strongly on the number of patients in the study. Simply including them as predictors in the generalized linear model is not viewed as an adequate consideration of their effect, because no evidence exists to suggest that they would be best modeled linearly, unlike LET effects. Analysis of additional patient data may eventually allow us to develop different models for patients at different ages at treatment and with different intervals between surgery and radiation therapy.

Interestingly, the selected treatment factors related to dose and LET were not found to be significant on multivariable analysis. This...
is not necessarily unexpected, because the entire purpose of carrying
out voxel-based data analysis was to overcome some of the
inherent problems of volume-based analysis. In this sense, the
image changes observed may be attributable to dose and LET
distributions in certain subvolumes of tissue, which would be difficult
to observe through whole-organ volume-based measures.

The high value of the cross-validated AUC is viewed as a good
indication that the model could be applied to patients outside this
cohort and still achieve favorable results. However, the intended
purpose of the model is not to specifically identify voxels that will
exhibit image change, but rather to provide a value for estimating
risk of change that can be used to optimize a treatment plan in
such a way as to reduce this risk. Using intensity modulated proton
therapy, which allows greater flexibility in plan optimization than
PSPT, the probability of image change provided by our model could
be used in treatment plan optimization as a constraint; indeed, this
is included in our own plans for future research. In addition, our
method is easily generalizable to any other anatomical site for
which a response can be identified by imaging. Here our model
was used only for MR image changes in the brain, but could be
expanded to other imaging modalities.

The current study was limited by the small number of patients
studied and its retrospective nature. To improve upon the results,
considerable further research can be done to improve the accuracy
of underlying data used in the analyses and to improve the accu-


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