Disregarding RBE variation in treatment plan comparison may lead to bias in favor of proton plans

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Purpose: Currently in proton radiation therapy, a constant relative biological effectiveness (RBE) equal to 1.1 is assumed. The purpose of this study is to evaluate the impact of disregarding variations in RBE on the comparison of proton and photon treatment plans.

Methods: Intensity modulated treatment plans using photons and protons were created for three brain tumor cases with the target situated close to organs at risk. The proton plans were optimized assuming a standard RBE equal to 1.1, and the resulting linear energy transfer (LET) distribution for the plans was calculated. In the plan evaluation, the effect of a variable RBE was studied. The RBE model used considers the RBE variation with dose, LET, and the tissue specific parameter $\alpha/\beta$ of photons. The plan comparison was based on dose distributions, DVHs and normal tissue complication probabilities (NTCPs).

Results: Under the assumption of $\text{RBE} = 1.1$, higher doses to the tumor and lower doses to the normal tissues were obtained for the proton plans compared to the photon plans. In contrast, when accounting for RBE variations, the comparison showed lower doses to the tumor and hot spots in organs at risk in the proton plans. These hot spots resulted in higher estimated NTCPs in the proton plans compared to the photon plans.

Conclusions: Disregarding RBE variations might lead to suboptimal proton plans giving lower effect in the tumor and higher effect in normal tissues than expected. For cases where the target is situated close to structures sensitive to hot spot doses, this trend may lead to bias in favor of proton plans in treatment plan comparisons. © 2014 American Association of Physicists in Medicine. [http://dx.doi.org/10.1118/1.4892930]

Key words: relative biological effectiveness, linear energy transfer, protons, radiobiological models, treatment planning

1. INTRODUCTION

The interest in proton radiation therapy is continuously growing as reflected by the increasing number of proton radiotherapy centers. This is mainly due to the physical properties of protons enabling highly conformal dose distributions. The lower dose, in comparison to photons, deposited by each proton beam to the proximal target border and the steep fall-off outside the distal target border have endorsed proton therapy for many clinical indications when organs at risk are close to the target. Furthermore, as the integral dose from protons to the normal tissue outside the target is substantially lower than for photons, proton therapy is also recommended as the modality of choice when larger volumes of normal tissue can be spared, which is especially important for pediatric patients. However, the superiority of protons over photons has not been tested in extensive clinical trials. In fact, the need of proving the effectiveness of proton therapy through randomized controlled clinical trials was debated to the point of questioning and deeming them unethical, due to the solid evidence of the physical properties of protons in interaction with tissue corroborated with the good clinical results.

Although larger randomized trials comparing photons and proton have not been performed, there are several treatment planning studies advocating for the potential advantage of radiotherapy with protons over photons, recent examples being the studies by van de Water et al. and Roelofs et al. However, when comparing treatment plans of photons and protons, the increased effectiveness of protons as compared to photons per unit dose has to be taken into account. Two dose distributions are equivalent only if the corresponding biological effects are the same, hence, biologically equivalent doses should be compared. To take advantage of the experience gained from conventional radiotherapy with photons, the proton dose is often expressed in terms of a biologically equivalent photon dose by multiplying the physical proton dose with its corresponding relative biological effectiveness, RBE. Accurate RBE values are therefore essential since an incorrect RBE value may propagate into an inappropriately chosen proton prescription dose, give another biological effect than expected, and overall leading to erroneous results.
in plan comparison. Currently, a constant RBE of 1.1 is usually assumed for protons, meaning that a given proton dose is assumed to be equivalent to a 10% higher photon dose. However, the RBE is not constant but has been found to vary with factors such as linear energy transfer (LET), dose per fraction, and tissue type. Thus, the distribution of RBE within the irradiated volume could be highly heterogeneous. There are several studies in which the differences in the proton plans created based on a constant RBE and on a variable RBE have been assessed showing considerable discrepancies. Howver, to the best of our knowledge, these studies compared different proton plans and did not include photon plans that were supposed to constitute the control arm in a typical clinical trial designed to assess the clinical effectiveness of protons versus photons.

In light of the development of several proton facilities in Europe in which the selection of individual patients for proton therapy will be performed based on a strict comparison of the proton plan to the best achievable optimized photon plan, the current study focuses on the comparison between proton and photon plans. The aim is to evaluate the impact on treatment plan comparison when the complex RBE dependence on LET, dose per fraction and tissue type is taken into account.

2. METHODS AND MATERIAL

In this study, intensity modulated treatment plans using photons (IMRT) and protons (IMPT), respectively, were created and compared for three brain tumor cases. The plans were generated in RayStation (RaySearch Laboratories, Stockholm, Sweden) using the delivery technique SMLC (step-and-shoot) for the photon plans, and pencil beam scanning with a Monte Carlo dose engine for the proton plans. The selected clinical brain tumor cases had the target situated close to the brain stem, optic chiasm, and optic nerve. Since the geometrical uncertainties were relatively small in these intracranial locations, this allowed preferentially studying the dosimetric effects of RBE.

The proton plans were optimized under the standard assumption of a RBE equal to 1.1 aiming to obtain a RBE-weighted dose to the tumor as high as in the corresponding photon plan or higher while keeping the dose to the normal tissue as low as in the photon plan or lower. In the plan comparison, the resulting proton plans with dose and LET distributions were evaluated accounting for the RBE variation. A previously published RBE-model that takes into account how RBE varies with dose, LET, and the tissue specific parameter $\alpha/\beta$ of photons was used. The plan comparisons were performed based on dose distributions, dose-volume histograms (DVHs) and normal tissue complication probabilities (NTCPs).

2.A. Treatment plan comparison

For each case considered, an IMRT plan was first created. In two cases (case 1 and case 2, see the top left and middle left panel in Fig. 1, respectively) seven equidistant beams were used, and in one case (case 3, see the bottom left panel in Fig. 1) nine equidistant beams were used. The prescription dose was 59.4 Gy delivered in 33 fractions. The maximum dose to critical structures, i.e., brain stem, optical nerve, and chiasm, was constrained to avoid hot spots.

An IMPT plan for each case was subsequently created with the beams angles shown in Fig. 1. A standard RBE value of 1.1 was assumed for the RBE-weighted dose in the plan optimization. The aim was to obtain the same RBE-weighted dose to the tumor as in the photon plan (59.4 Gy) or higher while obtaining an equally low dose to the normal tissue as in the photon plan or lower.

In the treatment plan comparison, the dose distributions obtained from photons and protons were compared by converting the proton dose to a biologically equivalent photon dose and studying the dose differences both when assuming a RBE-weighted proton dose with a RBE equal to 1.1, and when assuming a heterogeneous RBE. The physical proton dose distribution was thus identical so the RBE-weighted doses differed only by the assumed RBE. The DVHs and NTCPs resulting from the different RBE-weighted dose distributions were compared with the corresponding results obtained with photons.

2.B. LET calculation

The LET calculation was implemented in the already existing Monte Carlo dose engine framework for pencil beam scanning in the treatment planning system RayStation. The Monte Carlo code was specifically developed for proton transport calculations in the therapeutic energy range in voxelized geometries. Primary and later generations of protons are accounted for. The mass density in each voxel is obtained from the voxel grid and scoring its energy loss ($dE$) in each step with the step length $dx$ through the voxels. Energy lost by electronic interactions is accounted for. For each voxel $v$, the contributions from all protons, in all spots and beams per fraction are scored, and the dose averaged LET per voxel is calculated as

$$\text{LET}(v) = \frac{\sum_{\text{protons}} \frac{dE}{dx} \cdot \text{dose}}{\sum_{\text{protons}} \text{dose}}. \quad (1)$$

Thus, the LET is averaged by weighting the contribution of each proton by the dose it deposits in each step. In this study, the voxel volumes were $2.5 \times 2.5 \times 2.5 \text{ mm}^3$.

2.C. The RBE model and RBE-weighted dose calculations

A previously developed RBE model for protons was applied. The model was found to provide a significantly improved fit ($p$-value < 0.01) to experimental data compared to the standard constant RBE. It is derived from statistical exploration of empirical data and based on the classical linear quadratic model. The proton RBE is estimated from dose per fraction $d$, LET, and the tissue specific parameter $\alpha/\beta$.
The model predicts a tissue-dependent relation between RBE and LET determined by the $\alpha/\beta$ ratio: the RBE increases with increasing LET for cell lines with low $\alpha/\beta$ ratio, but the relation becomes weaker with increasing $\alpha/\beta$, and at high $\alpha/\beta$ ratios, RBE is close to 1 and relatively insensitive to LET changes. The implication is that late responding tissues ($\alpha/\beta \approx 3$ Gy) appear to be more sensitive to an increased LET than early responding tissues and most tumors ($\alpha/\beta \approx 10$ Gy). Moreover, the model shows an increasing RBE with
TABLE I. Radiobiological NTCP parameter values (Ref.11).

| Normal structures | D_{50} | γ | α/β | s   |
|-------------------|--------|---|-----|-----|
| Brain stem        | 65.1   | 2.4| 2.1 | 1.00|
| Optic nerve and chiasm | 65.0   | 2.3| 3.0 | 1.00|

decreasing dose per fraction and the effect is most pronounced for low α/β. Thus, the α/β parameter for photons is a predictor for the sensitivity to proton radiation, and the highest RBE values are predicted for cell lines and tissues with low α/β receiving high LET and low dose per fraction.

The dose distributions and the LET distributions were exported from the treatment planning system and imported into the computation software MATLAB (The MathWorks, Inc., MA) where the RBE distributions were calculated using Eq. (2). An α/β equal to 10 Gy was assumed for the tumor, and the values used for the different normal structures are given in Table I. The RBE-weighted total dose was calculated by multiplying the RBE-weighted dose per fraction by the total number of fractions.

2.D. Normal tissue complication model

The NTCP was estimated with the relative seriality model developed by Källman and co-workers with the response probability \( P \) calculated with the Poisson-based linear quadratic model

\[
\text{NTCP}_{\text{seriality}} = \left(1 - \prod_{i=1}^{M} (1 - [P(D_i)]^{s} v_i/V_{\text{ref}})\right)^{1/s},
\]

\[
= \left(1 - \prod_{i=1}^{M} (1 - [\exp(-\exp(e\gamma - \frac{\text{EQD2}}{D_{50}}(e\gamma - \ln(\ln(2))))])^{s} v_i/V_{\text{ref}})\right)^{1/s},
\]

(3)

where EQD2 is the equivalent dose given in 2 Gy fractions

\[
\text{EQD2} = \frac{D \left(1 + \frac{d}{\alpha/\beta}\right)}{1 + \frac{2}{\alpha/\beta}}.
\]

(4)

The total dose \( D \) and the fractional dose \( d \) denote physical photon doses or RBE-weighted proton doses. \( D_{50} \) is the dose giving a 50% response probability, \( \gamma \) is the maximum normalized gradient of the dose response curve, and \( s \) is the parameter describing the degree of seriality of the tissue, i.e., the volume effect of the tissue. \( M \) denotes the total number of voxels, and \( v_i/V_{\text{ref}} \) is the relative volume of voxel \( i \) compared to the reference volume. The parameter values used for the different organs at risk are presented in Table I.

3. RESULTS

Figure 1 shows the dose distributions obtained for the photon plans and the corresponding RBE_{1.1}-weighted dose distributions optimized for the proton plans according to the optimization criteria described in Sec. 2.A for all cases considered. The integral dose of the normal tissue is about the half (48% on average) in the proton plan compared to the photon plan in all cases. Figure 1 also shows the dose-averaged LET distribution of the protons plans. The LET distributions indicate that the highest values are obtained in the distal part of the proton beams.

Figure 2 presents the variable RBE distributions estimated from the LET distributions in Fig. 1 according to the RBE model used. Heterogeneous distributions were obtained with RBE higher than 1.1 in the brainstem and lower than 1.1 in the target. The resulting RBE-weighted dose distributions give a slightly larger integral dose to the normal tissue than when assuming a RBE equal to 1.1, but is still about half (51% on average) of the corresponding dose in the photon plan in all cases.

In Fig. 3, the difference in equivalent doses between proton plans and photon plans are compared. The physical proton dose distribution is the same in each brain case, only the RBE assumption differs. Under the assumption of RBE equal to 1.1 (shown in the left panels), the proton plans
generally show a slightly higher dose to the tumor and lower doses to the normal tissues as compared to the photon plans. In contrast, when a variable RBE is accounted for in the RBE-weighted proton dose distributions, the proton dose to the tumor is generally lower than the photon dose, and the dose to the adjacent brain stem is comparatively higher (see the right panels in Fig. 3). In the distal part of the brain stem, however, the proton dose is lower compared to the corresponding photon dose. The dose to the optic nerve is generally lower in the proton plan but there are hot spots compared to the photon plans (see Table II).

Figure 4 shows dose profiles for case 1 obtained from the photon plan, and the two different RBE-weighted proton doses from the location indicated by the horizontal line marked in Fig. 1. The proton-LET profile is also shown illustrating the increase in LET beyond the dose maximum. It is interesting to note that the photon-equivalent proton dose obtained when accounting for the RBE distribution shows a lower dose in the tumor compared to both the photon dose and the RBE$_{1.1}$-weighted proton dose, and an increased range compared to the RBE$_{1.1}$-weighted proton dose.

The differences in biologically equivalent doses shown above are also illustrated with DVHs for case 1 in Fig. 5. With the assumption of a constant RBE equal to 1.1, shown in the left panels, the proton plan gives higher equivalent doses to the tumor, while the normal tissue DVHs are shifted toward lower doses compared to the photon plan. The DVHs of the photon and proton plans are comparable in the high dose region. In the DVH comparison made with a RBE distribution, shown in the right panels of Fig. 5, the equivalent dose to the tumor is in contrast lower in the proton plan compared to the photon plan. The DVHs of the normal tissues show somewhat higher doses here compared to the RBE$_{1.1}$-weighted DVHs but are still well below the photon DVHs in general. However, in the high dose region, the DVHs of the normal tissues are shifted to higher doses in the proton plan as compared to the photon plan.

The differences in DVHs and dose distributions are also translated into different NTCP values, shown in Table III. As an example, the probability of necrosis in the brain stem is estimated in case 1 to 0.84% for the IMRT plan and 0.57% for the photon plan when assuming a RBE equal to 1.1. However, when assuming a variable RBE the probability increases to 2.13%. Equivalently, the probability for blindness increases from 1.13% (RBE = 1.1) to 4.21% (variable RBE) for protons compared to 1.21% for photons for the optic nerve. The same tendency of estimating a lower NTCP for protons compared to photons when having RBE equal to 1.1, but obtaining a higher NTCP compared to photons when assuming a RBE distribution is also observed for the chiasm and for the other brain cases (see Table III).

4. DISCUSSION

Disregarding RBE variations may lead to the creation of suboptimal proton treatment plans with lower than expected effect in the tumor and higher than expected effect in normal tissue. This trend may lead to bias in favor of proton plans in comparison to photon plans. Ultimately, accounting for the variable RBE in plan evaluation may reveal situations when the photon plan may be better than the proton plan optimized under the assumption of a constant RBE as shown for the brain cases studied in this work.

Since equal physical photon and proton doses do not give the same biological effect, biologically equivalent doses are essential in the comparison of treatment plans. This study
illustrates the importance of accounting for the variations in RBE. The largest difference in predicted response as a result of accounting for a variable RBE was found for late responding normal tissues that are sensitive to hot spots, situated close to the target. For these tissues, the combination of low fractional doses, high LET, and low $\alpha/\beta$ ratios could give a higher RBE than the recommended value of 1.1, and an extension of the bio-effective range of the protons leading to hot spots as illustrated by the results in Figs. 3 and 4. Even though the proton plans generally gave far lower biologically equivalent doses to normal tissues compared to the photon plan, regardless of whether a constant or a variable RBE is assumed, the hot spots in small volumes observed when accounting for a variable RBE generated predictions where the NTCP for protons were worse compared to those obtained for the photon plan. This is especially important for serial organs where the maximum biologically equivalent dose governs the response. Thus, the results in Table III show that despite the generally lower dose to the brain stem with protons as compared to photons, the maximum biological dose can be higher for protons leading to a worse predicted NTCP, which is undetected in the plan evaluation when not accounting for a variable RBE. This stresses the importance of accounting for the clinically relevant radiobiological details of particle therapy in order to avoid an increase in late reactions that could overwhelm the potential advantages.\textsuperscript{13}

Tumors may receive relatively high LET components in proton radiotherapy since Bragg peaks are placed inside the target volume. However, the biological effect of an increased LET depends on the $\alpha/\beta$ of the tissue as predicted by the RBE model used in this study.\textsuperscript{10} The high $\alpha/\beta$ equal to 10 Gy together with the clinically relevant dose per fraction given to the tumor resulted in a predicted biological effectiveness close to that of photons with a mean RBE of 1.06 for the three cases. This is lower than the RBE equal to 1.1 assumed in the treatment plan optimization. The consequence is that instead of the slightly higher biologically equivalent dose to the tumor in the proton plan compared to the photon plan as expected from the optimization, a lower dose to the tumor is obtained compared to photons in the evaluation when accounting for the RBE distribution (see Fig. 4). For other types of tumors that have low $\alpha/\beta$, such as prostate cancer, a very different result is expected.\textsuperscript{14} For these tumors the increased LET might lead to a significant gain, resulting in a RBE higher than 1.1.

The RBE predictions in this study were calculated based on model parameters obtained from \textit{in vitro} cell survival data for a range of different cell types irradiated with different doses and LETs. Since the model and its parameters were derived from limited empirical data, uncertainties in the experimental determination of cell survival and RBE will carry over to the model and its parameters. While the magnitude of the predicted effects might be debated, especially \textit{in vivo}, the trend toward a decreased effect in the tumor (high $\alpha/\beta$) and increased effect in the surrounding normal tissue (low $\alpha/\beta$) compared to the predictions from a constant RBE equal to 1.1 should still be valid. This is supported by the analysis of proton radiotherapy results in prostate patients performed by Dasu and Toma-Dasu\textsuperscript{14} who showed that the use of a variable RBE leads to closer predictions than the generic RBE $= 1.1$.

In order to take the full potential of proton radiation therapy into account, not only the improved dose distribution but also the biological effectiveness needs to be optimized and

![Fig. 4. Depth dose curves and depth LET curve.](image-url)
exploited. The increased effectiveness in the end of the proton beam can be indirectly addressed with margins and the choice of beam angles, but preferably the variable effectiveness should be accounted for directly. This could be achieved by accounting for the LET distribution, but since the LET-RBE relation of protons depends on tissue type,\textsuperscript{15} RBE models that account for variations due to LET, tissue type, and dose per fraction are useful. To maximize the advantages of protons, biological models should be incorporated into the treatment planning system to enable plan optimization directly from the point of view of the expected results. With such an approach, better proton treatment plans can be obtained, and the patients that would benefit most from proton therapy could be identified.

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