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EDITORIAL

Relating Proton Treatments to Photon Treatments via the Relative Biological Effectiveness—Should We Revise Current Clinical Practice?

Harald Paganetti, PhD

Department of Radiation Oncology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts

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In radiation oncology, treatments are prescribed based on the physics parameter of dose instead of outcome (ie, tumor control probability [TCP] or normal tissue complication probability [NTCP]), so that methods to relate dose or dose distributions to a biological endpoint are needed. The relationships between organ dose distributions and NTCP as well as between prescription dose and TCP are largely based on individual experience and to some extent on outcome data analyses (1).

When treating radiation therapy patients with protons, the difference in effect for a given dose relative to photons must be considered for prescription doses as well as dose constraints. This is done through the use of the relative biological effectiveness (RBE) (2). It allows proton treatments to benefit from the clinical experience gained with photons.

RBE = 1.1 as an Approximation

The RBE is defined as the ratio of the proton dose to the photon dose for a given level of effect. Conventionally, all treatments in proton therapy assume an RBE of 1.1, thus physical doses in proton therapy are reduced by ~10% compared to what one would administer with photons. The value of 1.1 is based on experimental data, mainly in animal systems obtained in the 1970s (2).

Evidence for a Variable RBE From Cell and Animal Systems

In vitro and in vivo studies have focused on various tissues or cell lines as well as on various different endpoints. Most data consider clonogenic cell survival in vitro, which sheds some light on RBE variations in patients with respect to TCP. For NTCP endpoints, their relevance is not clear. Although there could be various laboratory endpoints relevant to define a clinical RBE for early as well as late effects, lack of data requires that RBE variations deduced from cell survival data be considered not only for TCP but also for NTCP considerations. From these data, we know that the RBE varies as a function of dose, tissue (eg, α and β as the parameters of the linear quadratic dose-response relationship), and physics characteristics of the proton beam at the point of interest.

The RBE depends on dose: Cell survival curves using protons typically show a less pronounced shoulder (ie, a higher α/β compared to photon experiments). Consequently, the RBE increases with decreasing dose, at least in the domain where the linear quadratic dose-response curve is applicable. This has been generally confirmed in vitro and in vivo, although in some experiments, a reverse effect was seen (3). Interpretation of the dose dependency based on experimental data can be difficult because, for standard fractionation regimens, doses at or below 2 Gy are of

Reprint requests to: Harald Paganetti, PhD, Massachusetts General Hospital, 30 Fruit St, Boston, MA 02114. Tel: (617) 726-5847; E-mail: hpaganetti@partners.org

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interest, which corresponds to a region where typically few data points are taken, particularly for in vivo endpoints. Furthermore, the applicability of the linear quadratic dose-response relationship might be compromised because of hypersensitivity or adaptive response.

RBE depends on the considered endpoint: For clonogenic cell survival, there appears to be a trend that RBE increases with decreasing α/β, although there are substantial uncertainties in RBE data as a function of α/β (3). Generally, this would imply a higher RBE for late responding normal tissues than for tumor tissue, with exceptions such as prostate cancer where low α/β values have been reported. There could be a significant patient variability in α/β for a given site. A difference in RBE between tissues with an α/β of 2 versus an α/β of 20 could be on the order of 20% (3).

The RBE depends on linear energy transfer (LET): Generally, RBE increases with increasing LET, eventually reaches a maximum, and then decreases due to an overkill effect. This turning point is not reached for protons of clinical relevance. One can thus assume a monotone and more or less linear increase of RBE with LET for a given dose and α/β value. The LET increase as a function of depth in a proton beam causes an increase of RBE with depth (4) as well as a shift of the distal fall-off of a spread-out Bragg peak (SOBP) by $\sim$1 to 3 mm (5). On average, RBE can be considered between 1.1 and 1.15 from the entrance to the center of an SOBP, then increase to $\sim$1.35 at the distal edge, and increase to $\sim$1.65 in the distal fall-off (3). These values can vary substantially depending on the treatment field, particularly the modulation width.

So far, none of those dependencies are considered in proton therapy treatment planning because the uncertainties for individual tissues (and patients), doses, and beam characteristics might potentially be bigger than the magnitude of the effect to be corrected.

Evidence for a Variable RBE From Patient Data

It may eventually be feasible to extract tumor-specific RBE values from clinical data because target dose distributions are typically homogeneous for both modalities. For organs at risk, RBE estimations are hampered because dose distributions in proton therapy for critical structures are typically more heterogeneous compared to photon treatments. Organ effects are dependent on the dose distribution, and the mean target dose is not necessarily a valid approximation.

If RBE variations are clinically significant, there may be increasing rates of tumor recurrence in regions where the LET is particularly low, whereas the tissue is characterized by a high α/β value. It has been speculated that medulloblastoma patients could be underdosed due to an estimated α/β of approximately 28 Gy when using protons because the RBE could potentially be below 1.1 (6). Subsequently, patterns of failure in 16 of 109 patients treated with protons were analyzed (7). No indication was found that the RBE might have been overestimated in this sample size.

Other evidence could come from early or late effects in regions of low α/β and/or high LET. This would occur, for example, if an SOBP field ranges out in the brainstem when treating targets in the brain. Consequently, brainstem, and cervical spine toxicities (eg, necrosis) found in 4 of 111 medulloblastoma patients were analyzed (Giantsoudi et al, unpublished data). No clear correlation between elevated LET and regions of toxicity was found, yet the sample size is small.

Potential Clinical Impact of a Variable RBE

Results of RBE from experimental systems in vitro and in vivo indicate significant deviations from 1.1 for certain scenarios. For example, tumors with a very high α/β value could cause biologically equivalent doses on the order of 5% to 10% below the prescription doses, whereas tumors with very low α/β values such as prostate tumors might show an RBE substantially higher than 1.1, possibly 1.3 or more. It might be of little concern if the RBE is set conservatively, but it might impact the interpretation of clinical trials comparing protons and photons assuming an RBE of 1.1.

The RBE increases with depth and is likely higher than 1.1 in the terminal few millimeters of an SOBP. Because the planning target volume extends the prescribed high-dose region beyond the tumor, high LET regions could be located in organs at risk. Because planners are aware of this, beam angles are chosen carefully to avoid pointing beams directly toward a critical structure (also because of range uncertainties). In some clinical cases, pointing a beam toward the brainstem cannot be avoided, causing potential RBE values of more than 1.1 to a small area of the brainstem (8). This needs to be considered when defining constraints.

Because the RBE depends on dose and many sites are being considered for hypofractionation, we must be aware of a potential reduction of RBE, even below 1.1, due to a decrease of RBE with increasing dose.

Finally, more and more proton treatments are being administered by using active scanning techniques instead of passively scattered proton beams. It has been shown that LET distributions in beam scanning might show more pronounced variations compared to passive scattering deliveries and thus potentially higher RBE values particularly outside of the target (9).

Increasing Therapeutic Ratio by Using Variable RBE Values

As discussed above, variable RBE values might pose a challenge to treatment planning and to the interpretation of proton outcome, but RBE variations also provide an

opportunity to further optimize dose delivery and increase the therapeutic ratio.

Proton beam scanning allows delivery of intensity modulated proton beams. Here, the dose distributions for each field can be highly inhomogeneous, and a variety of plans can fulfill clinical constraints. It has been demonstrated that plans that are clinically equivalent in terms of dose can differ significantly in LET distribution (9, 10). Influencing the LET distribution while maintaining the dose distribution within constraints is particularly promising for complex shaped targets.

Conclusions

From experimental data it appears that 1.1 is an appropriate average value for proton RBE, in particular having the need for a conservative RBE for the target in mind (2, 3). Furthermore, there is currently no clear clinical evidence that the RBE deviates significantly from this value. The application of models to predict variable RBE values in treatment planning seems to be premature at this point due to scarce experimental data, weak clinical evidence regarding significance, and interpatient variability.

On the other hand, generic RBE adjustment for low α/β tissues and for RBE toward the distal edge should be considered at least for certain sites or beam arrangements. For instance, one might consider applying an RBE of 1.2 for the terminal 1 cm of an SOBP if the impacted tissue has an α/β below 3 Gy.

It is evident from laboratory experiments that RBE varies with dose, LET, and biological endpoint. It is thus important to analyze recurrences as well as toxicities with respect to potential RBE variations. Furthermore, the increased use of intensity modulated proton beams will most likely increase the variation in LET and thus potentially the variation in RBE within an irradiated volume. More clinical studies might thus lead to revisiting the current RBE strategy.

Interpatient variability in RBE might be on the same order of RBE variation as a function of dose, endpoint, or energy deposition characteristics. Biomarkers to define patient-specific RBE values could help increasing the therapeutic ratio in proton therapy.

There might be fundamental differences between photon- and proton-induced radiation effects on the molecular, cellular, and tissue level, as well as on proton-specific effects on gene expression, signaling, cell cycle disruption, and angiogenesis (11). It is naïve to assume that these can be normalized with a simple concept such as the RBE.

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