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Relative Biological Effectiveness Uncertainties and Implications for Beam Arrangements and Dose Constraints in Proton Therapy

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Current clinical implementation of proton radiation therapy assumes a constant relative biological effectiveness (RBE) value of 1.1 throughout the treatment field, for both the target and organs at risks. Although few in vivo clinical data suggest that this approximation is clinically significant, in vitro studies demonstrate the dependency of RBE on dose, fractionation, proton energy, and linear energy transfer, as well as patient radiosensitivity and definition of endpoint. This article provides a brief review on the principles and individual factors contributing to RBE uncertainties, with emphasis on clinical practice. Clinical considerations regarding the effect of RBE uncertainties and implications for beam arrangements in proton therapy treatment planning are discussed through clinical examples for treatments of prostate cancer and posterior fossa tumors as well as craniospinal irradiation for medulloblastoma. Approaches on biological optimization in proton therapy are presented, including a discussion on linear energy transfer-based optimization as an alternative method for biological optimization and its implementation both in multicriteria optimization and inverse optimization modules.
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Introduction

Radiation therapy prescriptions and constraints are typically based on dose, a physics parameter, rather than outcome parameters. Our main experience when defining dose-response relationships comes from photon therapy. Consequently, in order to use dose constraints and objectives from photon therapy, differences in dose-response between modalities such as photons and protons need to be corrected for. Proton therapy treatment planning is based on physical dose times a factor to account for the difference in biological effect at the same dose when treating with photons, ie the relative biological effectiveness (RBE).

The proton RBE is the ratio of the absorbed doses that produce the same biological effect (endpoint X Eq. (1)) between a reference radiation (eg, ^{60}Co x-rays or 6-MV photons) and proton irradiation.

$$\mathrm{RBE}(\mathrm{dose}, \mathit{e}\mathrm{ndpointX}, \text{proton beam properties}) = \frac{\mathrm{dose}_{\mathrm{reference}}(\mathrm{endpointX})}{\mathrm{dose}_{\mathrm{protons}}(\mathrm{endpointX})} \quad (1)$$

The currently used RBE in clinical practice is a constant value of 1.1 and was chosen as a conservative estimate (ie, lower limit in the center of the target) to ensure tumor coverage when relating proton to photon treatments. Nonetheless, studies have shown that the proton RBE depends on the dose level, proton energy (thus linear energy transfer [LET]) and other factors such as the radiosensitivity of the tissue.[1] Doses in proton therapy are prescribed as Gy(RBE).[2] Most proton RBE values were obtained through in vitro cell survival experiments conducted usually under uniform irradiation.[1,3] Thus, the definition of RBE is clinically most meaningful in regions of tissue that receive a uniform absorbed dose. In organs with inhomogeneous dose distributions, RBE can be quantified in a voxel and then extrapolated by considering the entire DVH. Assuming that the linear quadratic equation of dose response is a valid approximation, one can relate the RBE to α_x and β_x of the reference photon

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radiation, the α and β of the proton radiation and the proton dose per fraction, D_p

$$RBD\,(D_p,\alpha_x,\beta_p,\beta_p)=\frac{\sqrt{\alpha_x^2+4\beta_x D_p(\alpha_p+\beta_p D_p)}-\alpha_x}{2\beta_x D_p} \quad (2)$$

An alternative formulation can be found assuming α depending on the dose-averaged LET and β independent of radiation modality (Eq. (3)).[1] The dependency of β on LET is typically quite weak.

$$RBE\left(LET_d,\ D_p,\ [\alpha/\beta]_x\right) = \frac{1}{D_p}\left(\sqrt{\frac{1}{4}[\alpha/\beta]_x^2+[\alpha/\beta]_x\alpha(LET_d)/\alpha_x D_p+\beta(LET_d)/\beta_x D_p^2}-\frac{1}{2}[\alpha/\beta]_x\right) \quad (3)$$

Because the RBE depends on the photon reference radiation, the reference has to be stated when reporting RBE values. Ideally, RBE values are reported relative to 6-MV Linac machines. Most experimentally defined RBE values in literature have been given relative to ^{60}Co or kVp X-rays so that correction factors need to be applied.[1] For treatment planning considerations fractionation needs to be taken into account as well. Note though that fractionation effects[3,4] are, by definition, not included in the RBE formalism.

Uncertainties in RBE

RBE Dependency on LET

Distributions of LET in a patient geometry can be calculated using Monte Carlo simulations on a patient CT geometry.[5] Based on the continuous slowing down approximation, as proton energy decreases along the beam path the LET increases as a function of depth for each proton field in a patient. As many particles contribute to the total dose in a region of interest, either track-averaged or dose-averaged LET (LET_d) is typically used to quantify radiation quality.[6] In proton therapy, for a given dose and endpoint, RBE increases monotonically with those LET quantities. The increasing RBE with increasing depth becomes of concern for critical structures immediately downstream of the target area where the dose is still considerable.

Depending on the number of fields and intensity-modulated delivery, LET distributions can be highly inhomogeneous.[5,7,8] Due to various sources of uncertainties and margins added in treatment planning, high LET regions typically extend into normal tissues. Because the currently used RBE value of 1.1 is meant as a conservative average, we may underestimate the RBE in regions of high LET_d. This would be the case particularly at the end of range of a proton field.[9-11] Figure 1 shows distributions of dose and LET_d in a patient. For typical beam arrangements, LET_d values in patient geometries can be more than 10 keV/μm in the distal fall-off, but only between 1.5 and 4 keV/μm in the target.[5] Note that intrafractional and interfractional motion would most likely wash out LET hot spots to some extend (Fig. 2).

In treatment planning, RBE variations are often considered qualitatively similar to physics-related range uncertainties because elevated LET values occur near the end of range.[14] Recently, RBE variations were considered indirectly by optimizing the LET distribution, constraining the desired physical dose.[15]

RBE Dependency on Dose

For the region of interest in standard fractionation (2 Gy per fraction in the target and lower for organs at risk), the dose dependency of the RBE is difficult to assess from experimental data. The majority of in vitro experimental studies report cell survival focusing on doses between 2 and 10 Gy.[1] Furthermore, the validity of the linear-quadratic equation is unclear at doses below ~1 Gy and above ~10 Gy.[16-18]

There are limitations of the available experimental cell survival assays for large doses of radiation (surviving fractions less than about 10^{-3} are very challenging to measure). Models suggest an increase in RBE as dose decreases.[19] One would thus expect that hypofractionated regimens result in lower RBE values. Several theoretical studies have addressed the issue of spatial variations of RBE in patients[19-24] and have analyzed the effect of RBE on fractionation in proton therapy.[4,25,26]

RBE Dependency on Endpoint Considering Clonogenic Cell Survival

The RBE for clonogenic cell survival in vitro is expected to decrease with increasing $(\alpha/\beta)_x$ of the reference radiation. The rationale is the decreasing curvature of the dose-response curve with increasing LET. There have been concerns that we may over- or under-estimate the RBE for tissues with either high or low $(\alpha/\beta)_x$.[27-29] Thus, the largest RBE might be expected in late responding normal tissues.[30] Some tumors can have high $(\alpha/\beta)_x$ as well and might thus experience low RBE.[28] On the other hand, this trend predicts a higher RBE when treating, for example, prostate cancer.[31] For normal tissues with low $(\alpha/\beta)_x$ one might expect an increase in the risk for side effects. Quantifying these dependencies is challenging due to the difference in patient radiosensitivity due to, for instance, genomic factors. Furthermore, some types of cancer may have defects in DNA repair pathways that influence the RBE.[32-37]

RBE Dependency on Endpoint Considering Tumor Control Probability

The majority of experimental RBE data are on clonogenic cell survival. Cell survival might be seen as a valid surrogate for understanding RBE with respect to tumor control. However, there are various pathways leading to cell death, which is not caused by radiation-induced damage itself but a combination of damage and apoptosis or failure to complete mitosis. Furthermore, in hypofractionation regimens, there could be vascular damage contributing significantly to tumor control probability (TCP). There are very few in vivo studies related to tumor control. For example, the RBE for tumor growth delay of NFSa (fibrosarcoma) in mice was reported as ~0.8 (at ~30 Gy relative to 180 kVp x-rays; this translates to an RBE of ~1.0 relative to ^{60}Co).[38] The study of tumor growth delay of human hypopharyngeal squamous cell carcinoma cells in mice