UNCERTAINTY OF RBE MODEL IN PROTON RADIOTHERAPY BASED ON $\frac{\alpha}{\beta}$ RATIO AND LINEAR ENERGY TRANSFER*

Kinga Jeleń, Leszek Grzanka, Paweł Olko

Institute of Nuclear Physics Polish Academy of Sciences, 31-342 Kraków, Poland

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In proton radiotherapy, a constant value of the relative biological effect (RBE) is assumed in clinical practice. Many studies based on *in vitro* and *in vivo* experiments suggest that variable proton RBE would improve the treatment outcome. Several models based on data extracted from *in vitro* experiments relate RBE variations with linear energy transfer (LET) and $\frac{\alpha}{\beta}$ ratio in linear-quadratic (LQ) model. In our study, we selected Wedenberg model and extended it by adding prediction of RBE statistical distribution. Such an approach propagates uncertainties of *in vitro* cell experiments into higher level quantities such as RBE and dose-volume-histograms. The model outcome was a skew RBE distribution. The mean value of predicted RBE distribution is in agreement of few percent with the original Wedenberg model. The introduced model predicts RBE distribution which enables more precise inter-model testing than a simple comparison of mean values.

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1. Introduction

Living systems exhibit complex response to radiation during and after radiotherapy with protons beams. The response of cells measured as cell survival is strongly correlated with a radiation dose. Many other factors, including cell type, dose rate and beam energy have also a non-negligible effect on cell-survival. Despite variability of RBE [1], in clinical practice, a simplified approach with a constant 1.1 factor is currently used. Variable RBE is still pursued as a more advanced alternative to constant RBE approach. From many phenomenological models [2] of variable RBE, we have

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chosen to study the Wedenberg model [3]. It relates RBE with LET (L), dose (D) and tissue specific parameter $\left(\frac{\alpha}{\beta}\right)_X$

$$\mathrm{RBE}\left(D, L, \left(\frac{\alpha}{\beta}\right)_X\right) = \frac{-\left(\frac{\alpha}{\beta}\right)_X}{2D} + \frac{1}{D}\sqrt{\frac{1}{4}\left(\frac{\alpha}{\beta}\right)_X^2 + \left(qL + \left(\frac{\alpha}{\beta}\right)_X\right)D + D^2}\,. \tag{1}$$

The model has a free parameter q which is best-fitted to the experimental data of cell survival irradiated in *in vitro* conditions.

The aim of our work is to extend the model prediction by adding a forecast of the distribution of RBE factor, in place of a single value. Such an approach would aid decision making in radiotherapy by adding new dimensions in the plan comparison and robustness evaluation.

2. Materials and methods

The extended model is based on replacing the free parameter q with a probability distribution derived from uncertainties of underlying experimental data. We achieved this by fitting linear-quadratic model parameters (α and β), retrieving best-fitted values along with fit accuracy and parameter correlation. We used a bootstrapping technique to propagate the uncertainties (assuming normal distributed errors) from training data to the model free parameters. Training data set is based on experimental data (see references in [3]) for 10 different cell lines irradiated with monoenergetic proton beams of kinetic energy ranging from 0.88 MeV to 5.04 MeV (corresponding to LET from 7.7 $\frac{\mathrm{keV}}{\mu\mathrm{m}}$ to 30.0 $\frac{\mathrm{keV}}{\mu\mathrm{m}}$). It contains also reference survival curves, obtained from ^{60}Co irradiations. Data set was cleaned by rejecting outlying points and measurements with insufficient statistics (less than 4 points per survival curve). For each data set, we performed numerical fitting of linear quadratic model. We used the Levenberg–Marquardt algoritm implemented in python library lmfit. Individual data points along with their uncertainties were used to obtain the α and β best-fitted values and covariance matrix M. Fit quality parameters (standard deviation of α and β normal distribution) along with correlation parameter were extracted from M. The original Wedenberg model relied on best-fitted value q according to (2)

$$q = \left(\frac{\alpha}{\alpha_X} - 1\right)\left(\frac{\alpha}{\beta}\right)_X\,. \tag{2}$$

We used the same formula, but instead of best-fitting a single value of parameter q, we derived its distribution from α, α_X and β_X (Fig. 1). The bootstrapping method was used on the data set consisting of 19 survival

curves, sampling was performed 10^6 times to obtain reasonable statistics. Despite assumed normal distribution of LQ model parameters, nonlinearity of the model (2) was responsible for skewed distribution of q. Similar method was used to derive distribution of RBE based on distribution of q, following the Wedenberg model formulation (1). Sampling was performed 10^6 times.

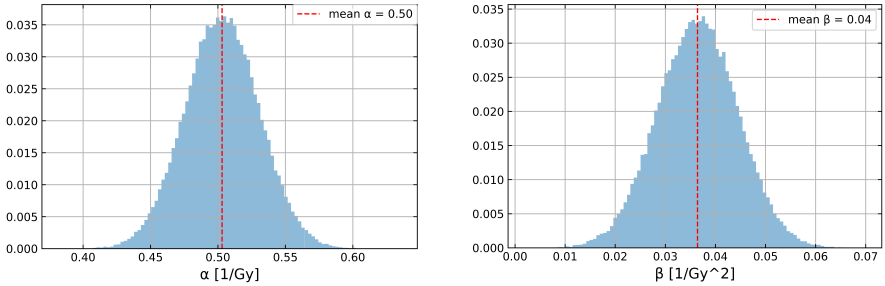

Fig. 1. Distributions of α and β parameters of LQ model fitted to cell survival data of Chinese hamster V79 cells irradiated with protons of energy 1.41 MeV.

3. Results

Propagation of uncertainties allowed us to obtain distribution of the Wedenberg model parameter q with median 0.393 which is in 3σ agreement with Ref. [3]. A comparison of RBE and biological dose was set up on a

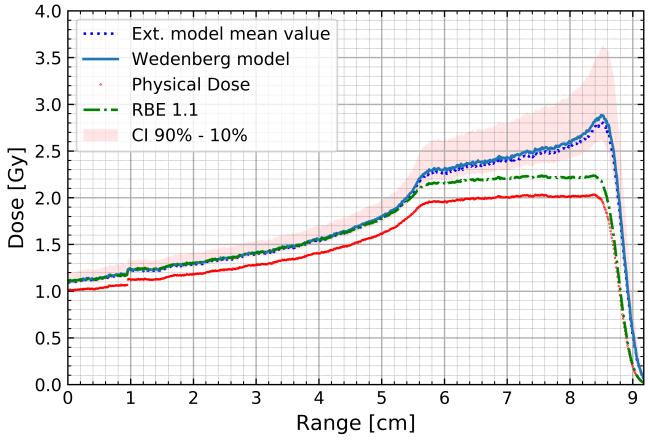

Fig. 2. (Colour on-line) Depth profiles of physical and biological dose [Gy] (grey/blue dots — biol. dose from extended Wedenberg model (mean value), black/blue solid line — biol. dose from original Wedenberg model, grey/green dot-dashed — physical dose multiplied by constant RBE 1.1, grey/red dot — physical dose, shaded area — confidence interval 90% for extended model predictions).

similar depth-dose and LET profile as being used in radiobiological *in vivo* mouse experiments (see [4]). A homogeneous dose was delivered to an area between depth 5.5 and 8.5 cm. RBE and biological dose calculated using the extended Wedenberg model was in agreement with original model within 2σ confidence interval (Fig. 2). In the middle of irradiated area, RBE was estimated to be 1.19. Our results correspond to data in Ref. [5].

4. Discussion

Plan selection, inter-plan comparison and robustness studies are necessary to achieve optimal treatment outcome in personalized radiotherapy. In state-of-the-art planning, certain metrics such as dose-volume, histogram can be used to aid plan comparison. Most of them are, however, based on expected value prognosis. Uncertainty related to biological variability is managed by a worse-case scenario approach [5]. We propose to introduce new dimension in the plan comparison studies: in addition to safety margins, we include biological variability represented as statistical distribution of the RBE factor. Such an approach follows closely research presented in [5] but is applied solely on the ground of a single radiobiological model. We believe that a development of statistical approach (*i.e.* applying Bayesian inference) may enrich decision-making process by providing more insight into biological variability.

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