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ORIGINAL ARTICLE

A model for the relative biological effectiveness of protons: The tissue specific parameter α/β of photons is a predictor for the sensitivity to LET changesMINNA WEDENBERG^{1,2}, BENGT K. LIND¹ & BJÖRN HÅRDEMARK²¹Medical Radiation Physics, Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden, and²RaySearch Laboratories, Stockholm, Sweden**Abstract**

Background. The biological effects of particles are often expressed in relation to that of photons through the concept of relative biological effectiveness, RBE. In proton radiotherapy, a constant RBE of 1.1 is usually assumed. However, there is experimental evidence that RBE depends on various factors. The aim of this study is to develop a model to predict the RBE based on linear energy transfer (LET), dose, and the tissue specific parameter α/β of the linear-quadratic model for the reference radiation. Moreover, the model should capture the basic features of the RBE using a minimum of assumptions, each supported by experimental data. **Material and methods.** The α and β parameters for protons were studied with respect to their dependence on LET. An RBE model was proposed where the dependence of LET is affected by the $(\alpha/\beta)_{\text{phot}}$ ratio of photons. Published cell survival data with a range of well-defined LETs and cell types were selected for model evaluation rendering a total of 10 cell lines and 24 RBE values. **Results and Conclusion.** A statistically significant relation was found between α for protons and LET. Moreover, the strength of that relation varied significantly with $(\alpha/\beta)_{\text{phot}}$. In contrast, no significant relation between β and LET was found. On the whole, the resulting RBE model provided a significantly improved fit (p -value < 0.01) to the experimental data compared to the standard constant RBE. By accounting for the α/β ratio of photons, clearer trends between RBE and LET of protons were found, and our results suggest that late responding tissues are more sensitive to LET changes than early responding tissues and most tumors. An advantage with the proposed RBE model in optimization and evaluation of treatment plans is that it only requires dose, LET, and $(\alpha/\beta)_{\text{phot}}$ as input parameters. Hence, no proton specific biological parameters are needed.

The number of proton therapy centers is increasing and to date there are more than 30 facilities worldwide that have treated more than 65 000 patients in total [1]. The primary advantage of proton therapy over conventional radiotherapy with photons and electrons is that the dose can be more focused to the tumor. Proton beams are considered especially well-suited for irradiation of, e.g. tumors located close to critical, radiosensitive structures in cases where the steep dose fall-off at the distal end of the proton range is advantageous, and for pediatric tumors due to the reduced integral dose. While the physical properties of proton beams are relatively well known, there are still questions regarding their biological effects. To take advantage of the experience gained

from conventional radiotherapy with x-rays, the biological effects of particles are often expressed in relation to that of photons. The conversion from a (physical) particle dose to a (biological) photon equivalent dose is made using the concept of relative biological effectiveness (RBE). The physical proton dose multiplied with the RBE gives the biologically equivalent photon dose, or the so called effective dose. Equivalently, the prescription dose of protons can be determined by dividing the intended photon dose by the RBE. Therefore, it is essential that a correct RBE value is used since an incorrect RBE value may result in another effective dose than intended with a discrepancy larger than the dose accuracy of $\pm 3\%$ usually requested [2]. Also, an incorrect

RBE value may propagate into an incorrectly chosen proton prescription dose.

There is experimental evidence that the RBE varies with the linear energy transfer (LET), the dose, the cell or tissue type, and the chosen endpoint [3]. However, currently in proton therapy, a generic RBE of 1.1 is usually applied [4] regardless of the physical properties of the proton beams and the biological system. This means that a given proton dose is assumed to be equivalent to a 10% higher photon dose for all tissues, tumors, doses and energies. A constant RBE is recommended in the report by the International Commission on Radiation Units and Measurements (ICRU) [5], but in the same report it is warned for the increased RBE at the distal end of the proton range. A constant RBE for protons is a simplification and values both higher and lower than 1.1 have been observed. The use of a constant RBE has largely been due to the relatively small differences in RBE together with relatively large uncertainties in the experimentally obtained RBE values and considerable variations across experiments which make it difficult to discover systematic trends between different beam setups and biological systems [5]. In this study, we will investigate if more clear trends in the variation of RBE are revealed by accounting for cell type.

One way of characterizing the cell type or tissue type in terms of sensitivity to radiation is by the parameters α and β of the well-known linear-quadratic (LQ) model [6]. A low α/β ratio after exposure to photons has been found to be associated with late-responding tissues whereas a high α/β ratio is linked to early-responding tissues and most tumors. Therefore, the α/β ratio has an impact on dose fractionation effects and has been established and tabulated for many tissues and tumors. One question addressed in this study is if the cells' sensitivity to photon radiation, quantified by the α/β ratio, can be used to estimate their sensitivity to proton radiation.

There are several cell survival studies where the parameters of the LQ model for protons are obtained, and several research groups have studied the dependence of these parameters on LET. A linear dependence of α as a function of LET up to LET values around RBE maximum have been suggested by, e.g. Hawkins [7], Wilkens and Oelfke [8], and Tilly et al. [9]. The LET dependence of β is less clear with some studies pointing to an increasing β with increasing LET [10,11] whereas others report a decreasing trend [12,13]. Often a constant β is assumed for protons [8,9,14].

A cell dependence of the parameter α has been suggested in various forms. Tilly et al. [9] used two discrete slopes of the linear dependence on LET depending on which α/β ratio of the reference radi-

ation the cell was grouped into ($\alpha/\beta \approx 2$ or ≈ 10). Dale and Jones [14] introduced a parameter RBE_{\max} , defined as the ratio of α for high LET over α for low LET, which depends on dose and the α/β ratio of the low-LET radiation (but no LET dependence is included). Hawkins [7] and Frese et al. [15] use an α/β ratio-dependence within the framework of the microdosimetric-kinetic model and the repair-misrepair-fixation model, respectively. Other models have a free parameter that needs to be determined for each cell type [8].

The aim of this study is to develop a model to predict the RBE for protons based on dose, LET, and the tissue specific parameter α/β of photons. Moreover, the model should capture the basic features of the RBE, using a minimum of assumptions that are supported by experimental data. The α and β parameters will be studied with respect to their dependence on LET. We hypothesize: 1) a linear relation between α and LET; with 2) a slope that depends on cell type where the cell type is represented by the α/β ratio of photons; and finally, 3) we assume a parameter β independent of LET. Statistical analyses of experimental data will be performed to verify the validity of these assumptions. In order to study how the parameters α and β vary with LET and cell type, published in vitro clonogenic cell survival data where the LET and cell type are well-defined were chosen.

Material and methods

The RBE model

A first expression of the RBE can be derived from the LQ model, which describes the survival fraction as a function of dose and the radiosensitivity parameters α and β , together with the definition of RBE (see Appendix: available online at <http://www.informahealthcare.com/doi/abs/10.3109/0284186X.2012.705892>). This expression includes three ratios of interest: $(\alpha/\beta)_{\text{phot}}$, α/a_{phot} , and $\beta/\beta_{\text{phot}}$. The subscript phot will denote the reference photon radiation (e.g. ^{60}Co γ -rays or x-rays) in this report whereas all other quantities pertain to proton radiation unless otherwise stated. The first quantity $(\alpha/\beta)_{\text{phot}}$ is simply the ratio of the LQ parameters from photon exposure which is often used to characterize the radiosensitivity of a cell type or tissue. For the other two ratios, analytical expressions are proposed to describe how they vary with LET, and then evaluated using statistical methods (see Parameter estimation and model evaluation).

The ratio α/a_{phot} has shown to increase with increasing LET up to around 30 keV/ μm for protons, after which it decreases [10]. Exactly how α/a_{phot}

increases with LET is not fully determined. There are few publications that report a for monoenergetic proton beams especially for LETs < 5 keV/ μ m. Due to the limited number of experimental data sets, a simple linear dependence to the LET, L , is assumed here where a for protons approaches a_{phot} for photons, when LET decreases:

$$\frac{a}{a_{\text{phot}}} = 1 + kL \quad (1)$$

Equation 1 is not valid for LETs higher than 30 keV/ μ m since it does not account for the decrease at higher LETs. However, that high values are of little practical relevance with the energies used in clinical proton therapy due to straggling effects and, therefore, not considered in this work. Different studies report different a/a_{phot} values for similar LET values. The difference is possibly due to differences between cell lines. We assume that the slope k is affected by the cell type and propose an inverse relationship between the slope and the tissue response related parameter $(a/\beta)_{\text{phot}}$ so that k decreases as $(a/\beta)_{\text{phot}}$ increases (see Equation A6 in Appendix). This means that the cell survival of cell lines with high $(a/\beta)_{\text{phot}}$ ratio depends less on LET because of the smaller slope k compared to cell lines with low $(a/\beta)_{\text{phot}}$. The resulting expression for a/a_{phot} becomes

$$\frac{a}{a_{\text{phot}}} = 1 + \frac{qL}{(a/\beta)_{\text{phot}}} \quad (2)$$

where q is a free parameters of the expression.

The dependence of the ratio $\beta/\beta_{\text{phot}}$ on LET is more unclear since different research groups come to different conclusions. On this basis, the correlation between β and LET seems weaker than that for a and we will assume a constant β equal to β_{phot} , *i.e.* $\beta/\beta_{\text{phot}} = 1$.

The resulting expression for the RBE, obtained by inserting the expression for a/a_{phot} (Equation 2) and $\beta/\beta_{\text{phot}} = 1$ into the original RBE expression (Equation A4 in Appendix), depends only on the proton dose, LET, and a/β ratio of photons:

$$\begin{aligned} RBE(D, L, (a/\beta)_{\text{phot}}) = & -\frac{1}{2D} \left(\frac{a}{\beta} \right)_{\text{phot}} + \\ & \frac{1}{D} \sqrt{\frac{1}{4} \left(\frac{a}{\beta} \right)_{\text{phot}}^2 + \left(qL + \left(\frac{a}{\beta} \right)_{\text{phot}} \right) D + D^2} \end{aligned} \quad (3)$$

The constant q is the same regardless of the physical characteristics of the proton beam and the biological system. This expression is for single doses or dose per fraction.

Parameter estimation and model evaluation

For the purpose of our study, published clonogenic cell survival data with well-defined LET and reported a , a_{phot} , β , and β_{phot} values, were selected for the model evaluation. Experimental data of 10 different cell lines were included where the cells had been irradiated with near monoenergetic proton beams with LET values ranging from 6 to 30 keV/ μ m, *i.e.* up to LET values in the region of RBE maximum, giving in total 24 experimental data points [10–13,16,17]. All the cell lines with their experimental a and β values used in this study are tabulated in Table I.

The study by Perris et al. [18] met our criteria of selection but was not included in our study. They studied the survival of Chinese hamster V-79 cells following irradiation with monoenergetic protons and ^{60}Co γ -rays as a reference radiation. However, they report an $(a/\beta)_{\text{phot}}$ ratio of 25 which is far from the values around 5 that usually are reported for V-79 cells. A possible explanation could be that the cells were irradiated in different growth conditions. Due to the large discrepancy to other V79 cell lines, we omitted these experimental data.

To determine if the general assumptions made in the RBE model are adequate and supported by the experimental cell survival data, a series of statistical analyses were carried out. The significance level was set consistently to 5%. First, linear regression was used to test the assumption that there exists a positive relationship between a/a_{phot} and LET. The null hypothesis was that the slope equals zero. Additionally, a 95% confidence interval (CI) for the intercept of this linear relation was constructed to determine if the assumption that the intercept equals one is adequate.

Second, the influence of cell type to the dependence between a/a_{phot} and LET was studied. The assumption that the slope k from the linear relation between a/a_{phot} and LET changes with $(a/\beta)_{\text{phot}}$ ratio was tested with Vuong's test for non-nested models. This is a method for model selection based on the likelihood ratio test statistic. The models to be compared here are the expression derived in this study where the slope is assumed to vary with the $(a/\beta)_{\text{phot}}$ ratio, Equation 2, and the expression where the slope is constant, Equation 1. The null hypothesis is that these models are equally close to the "true" model (a theoretical, unknown model that provides a perfect fit do data) against the alternative hypothesis that one model is closer than the other. Vuong's test gives a test statistic that follows a standard normal distribution, so that a test statistic > 1.96 favors the $(a/\beta)_{\text{phot}}$ -dependent expression in Equation 2 over the $(a/\beta)_{\text{phot}}$ -independent expression in Equation 1 at

Table I. The cell lines used in this study with the published a and β values given in the order of increasing a/β of the reference radiation.

cell line	LET [keV/ μ m]	a [Gy $^{-1}$]	β [Gy $^{-2}$]	Reference
V79-379A	240 kV x-rays	0.13 ± 0.022	0.048 ± 0.003	[12]
	10.1	0.32 ± 0.058	0.039 ± 0.011	
	17.8	0.45 ± 0.035	0.028 ± 0.006	
	27.6	0.74 ± 0.025	0.011 ± 0.004	
V79-753B	200 kV x-rays	0.129 ± 0.012	0.046 ± 0.003	[10]
	7.7	0.289 ± 0.023	0.024 ± 0.006	
	11.0	0.372 ± 0.032	0.036 ± 0.009	
	20.0	0.469 ± 0.029	0.043 ± 0.009	
DLD1	^{60}Co γ -rays	0.37 ± 0.09	0.12 ± 0.02	[17]
	7.7	0.47 ± 0.05	–	
SQ20B	^{60}Co γ -rays	0.13 ± 0.02	0.017 ± 0.002	[13]
	7.7	0.15 ± 0.05	0.011 ± 0.012	
	19.8	0.23 ± 0.04	0.004 ± 0.007	
	30.0	0.57 ± 0.05	–	
C1-1	^{60}Co γ -rays	0.23 ± 0.042	0.030 ± 0.008	[16]
	7.7	0.194 ± 0.072	0.023 ± 0.021	
	27.6	0.539 ± 0.027	–	
C3H10T1/2	^{60}Co γ -rays	0.24 ± 0.06	0.016 ± 0.013	[11]
	11.0	0.47 ± 0.06	0.019 ± 0.014	
	19.7	0.43 ± 0.06	0.038 ± 0.013	
	28.8	0.55 ± 0.12	0.053 ± 0.031	
SCC25	^{60}Co γ -rays	0.57 ± 0.05	0.031 ± 0.012	[13]
	7.7	0.41 ± 0.11	0.092 ± 0.036	
	19.7	0.87 ± 0.05	–	
	29.5	0.81 ± 0.03	–	
HCT116	^{60}Co γ -rays	1.39 ± 0.06	0.02 ± 0.01	[17]
	7.7	0.32 ± 0.08	0.06 ± 0.03	
H184B5 F5-1M/10	^{60}Co γ -rays	0.52 ± 0.02	–	[13]
	9.1	0.50 ± 0.03	–	
	21.4	0.49 ± 0.02	–	
HF19	^{137}Cs γ -rays	0.64 ± 0.02	–	[13]
	7.7	0.55 ± 0.01	–	
	19.5	0.54 ± 0.02	–	
	29.0	0.52 ± 0.01	–	

the 5% significance level. As a complement to this analysis, to test for which cell types the slope is significantly larger than zero, the experimental data were grouped into four groups depending on their $(a/\beta)_{\text{phot}}$ ratio (2.7–3.1, 7.7–7.7, 15–18 and ≥ 70). The slope was studied in each group.

Finally, the assumption that there is no relation between $\beta/\beta_{\text{phot}}$ and LET was tested by constructing a 95% CI for the slope of the regression line.

For the derived model, the expression of a/a_{phot} , Equation 2, was fitted to the experimentally obtained a/a_{phot} ratios with least square optimization for all the cell lines and LETs used in this study to get a global value of the parameter q , i.e. a constant value regardless of the cell types and LET values used.

The resulting RBE model, Equation 3, was then evaluated by comparing the analytically obtained RBE values with experimental RBE values, and the model was further characterized by studying the effects of varying its input parameters.

Results

The results from the statistical analyses of the assumptions made in the RBE model show a positive relation between a/a_{phot} and LET; for the whole data set, the slope k was greater than zero with statistical significance with a one-tailed p-value < 0.05 . When grouping the experimental data based on the cell type, here measured by the $(a/\beta)_{\text{phot}}$ ratio, the slope was statistically greater than zero at the 5% significance level for the two groups with low $(a/\beta)_{\text{phot}}$ ratios (2.7–7.7). On the other hand, for the two groups with high $(a/\beta)_{\text{phot}}$ ratios (≥ 15) where the slope is smaller, the null hypothesis could not be rejected. The 95% CI for the intercept in the linear relation between a/a_{phot} and LET was 0.79 ± 1.1 , which includes the assumption of an intercept equal to one.

In the analysis on whether the relation between a/a_{phot} and LET is influenced by the cell type, i.e. the assumption of a varying slope k depending on the

$(a/\beta)_{\text{phot}}$ ratio, the Vuong's test resulted in test statistic of 2.7. Hence, the expression including a slope k that vary with $(a/\beta)_{\text{phot}}$, Equation 2, gives a statistically significantly better fit to the experimental data compared to the expression with a constant slope k , Equation 1, at the 5% significance level.

For the $\beta/\beta_{\text{phot}}$ ratio no statistically significant relation with LET was seen and the 95% CI for the slope was -0.01 ± 0.05 , which includes zero.

The value of parameter q of Equation 2 that best fitted the experimental a/a_{phot} data was found to be 0.434 [95% CI (0.366, 0.513)] ($\text{Gy } \mu\text{m}/\text{keV}$). This q value is used in all the figures in this study. The a/a_{phot} dependence on LET and $(a/\beta)_{\text{phot}}$ is visualized in Figure 1. The resulting slopes of the curves shown in the figure are presented in Table II. Generally, a/a_{phot} increased with increasing LET, but this relation between a/a_{phot} and LET was influenced by the $(a/\beta)_{\text{phot}}$ ratio. The sharpest increase was seen at low $(a/\beta)_{\text{phot}}$ ratios (panel A in Figure 1), but for very high $(a/\beta)_{\text{phot}}$ ratios a/a_{phot} displayed no trend with LET (panel D in Figure 1). Figure 1 shows that with increasing $(a/\beta)_{\text{phot}}$ ratio the slope k decreases, and in Figure 2 k as a function of the $(a/\beta)_{\text{phot}}$ ratio, obtained with Equation A6 in Appendix, is shown.

The comparison between the analytically obtained RBE values from the proposed model presented in

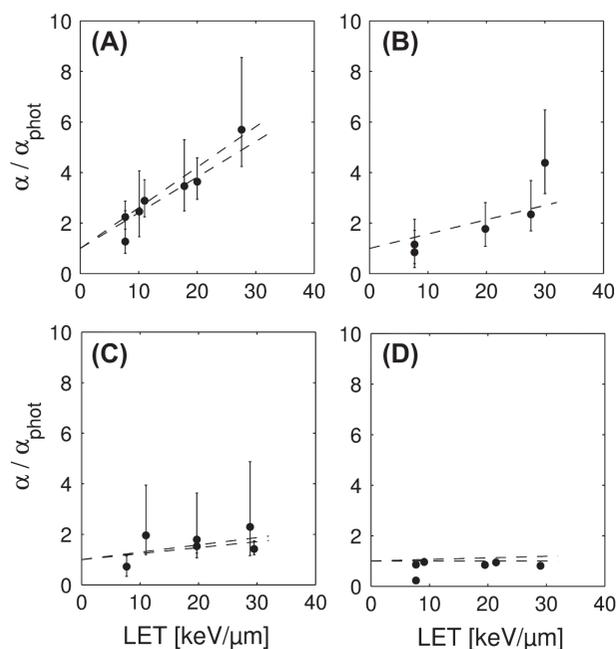


Figure 1. Experimentally obtained a/a_{phot} values as a function of LET. Panel A with $(a/\beta)_{\text{phot}}$ 2.7–3.1: V79-379A cells [12], V79-753B cells [10], and DLD1 cells [17]. Panel B with $(a/\beta)_{\text{phot}}$ 7.7–7.7: SQ20B [13], and C1-1 cells [16]. Panel C with $(a/\beta)_{\text{phot}}$ 15–18: C3H10T1/2 [11], and SCC25 [13]. Panel D with $(a/\beta)_{\text{phot}} \geq 70$: HCT116 [17], M/10 cells and HF19 cells [13]. The error bars show the 95% CI. The dashed lines are obtained with Equation 2 where the highest and lowest $(a/\beta)_{\text{phot}}$ in each panel is used.

Table II. The resulting slope k of Equation A6 used in Figure 1.

$(a/\beta)_{\text{phot}}$ [Gy]	k [$\text{keV}/\mu\text{m}$] ⁻¹
2.7–3.1	0.14–0.16
7.7–7.7	0.057–0.057
15–18	0.024–0.029
70–∞	0–0.0060

Equation 3 and the experimental RBE values is shown in Figure 3. The resulting coefficient of determination r^2 for RBE values of all cell lines and LETs was 0.76. The RBE model gave a statistically significantly better fit to data, compared to the standard model, which assumes a constant RBE. The resulting p-value was < 0.01 . In Figure 3, the RBE for the cell lines with the lowest and highest $(a/\beta)_{\text{phot}}$ ratio, 2.7–3.1 and ≥ 70 , respectively, are shown displaying a higher RBE for the cells with low $(a/\beta)_{\text{phot}}$ ratio than for the cells with high $(a/\beta)_{\text{phot}}$ ratio. For cells with low $(a/\beta)_{\text{phot}}$ ratio, the RBE increased with increasing LET whereas no such trend was seen for the cells with high a/β_{phot} ratio. In fact, the experimental RBE values for the cell lines with very high $(a/\beta)_{\text{phot}}$ ratio were smaller than unity. In Figure 4, the analytically obtained RBE values for all cell lines and LETs are compared with the experimental RBE values. Pearson's correlation coefficient was 0.89. Both in Figures 3 and 4, the RBE at the survival level obtained for the reference radiation at 2 Gy was used.

Figure 5 shows how the input parameters $(a/\beta)_{\text{phot}}$, dose, and LET of Equation 3 affect the RBE. The RBE generally increased with decreasing $(a/\beta)_{\text{phot}}$, with decreasing dose, and with increasing LET, but

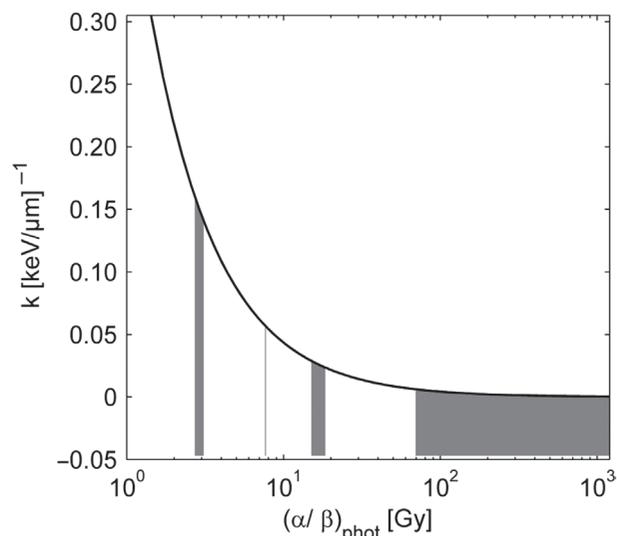


Figure 2. k is the slope from the linear relation between a/a_{phot} and LET (see Equation 1) and is here plotted as a function of the a/β ratio of the reference radiation using Equation A6 in Appendix with the parameter $q = 0.434$. The shaded areas under the curve show the $(a/\beta)_{\text{phot}}$ ranges used in the different panels of Figure 1.

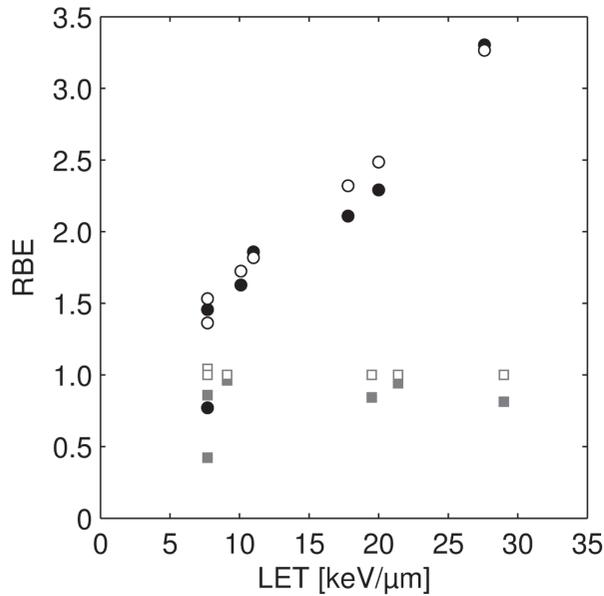


Figure 3. RBE as a function of LET at 2 Gy photon dose for cell lines with $(\alpha/\beta)_{\text{phot}}$ ratio < 4 (circles) and $(\alpha/\beta)_{\text{phot}}$ ratio ≥ 70 (squares). The experimental data is shown with filled symbols and the calculated data from Equation 3 has open symbols.

at high $(\alpha/\beta)_{\text{phot}}$ the change in RBE between different doses and LETs was small. Similarly, at low LETs and high doses, the RBE change due to variations in $(\alpha/\beta)_{\text{phot}}$ was small.

Discussion

We have developed an RBE model that is able to estimate the RBE for protons. The proposed model

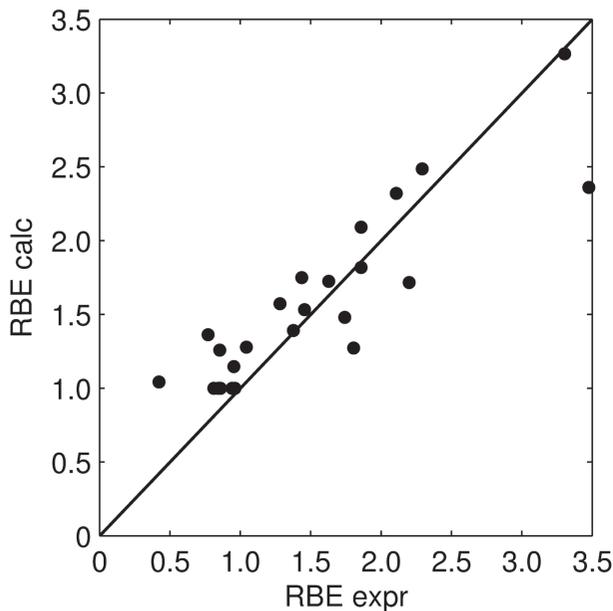


Figure 4. Analytically obtained RBE values (see Equation 3) vs. experimental RBE values for all cell lines used in this study. Pearson’s correlation coefficient is 0.89. The RBE is obtained at 2 Gy photon dose.

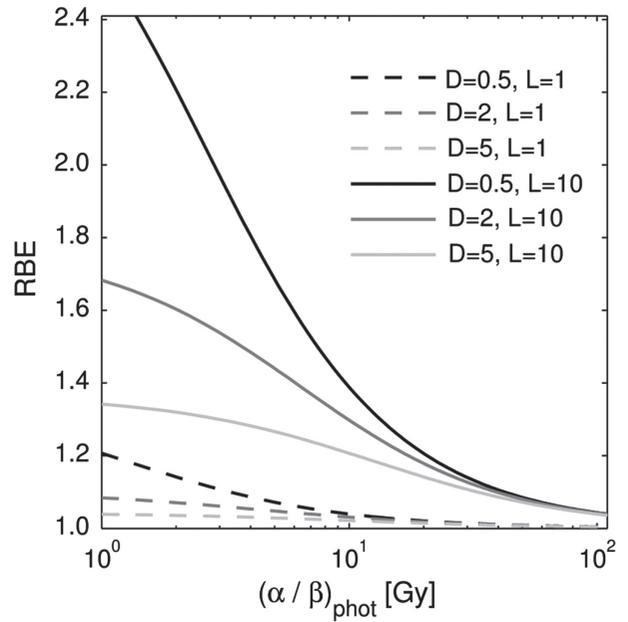


Figure 5. RBE as a function of α/β of the reference radiation using Equation 3. Three doses, 0.5, 2 and 5 Gy, and two LETs, 1 and 10 keV/μm, are compared.

is simple in the way that it is based on the well-known linear-quadratic model and the only information needed is the dose, LET, and the α/β ratio of the reference radiation. The constant q is the same regardless of the physical characteristics of the proton beam and the biological system. Hence, no proton specific biological parameters are needed. With this model, investigations on how the RBE is affected by changes in dose, LET, and cell type can easily be made.

With the aim to develop a model using few assumptions that are supported by experimental data, statistical analyses were made to test our expressions. A statistically significant positive relation between the experimental a/a_{phot} values and LET was found, which supports our first assumption that a/a_{phot} increases with increasing LET. The 95% CI for the intercept of that relation included our assumed value of one, even though the spread was large. From the experimental data included in this study, it is difficult to determine exactly how a/a_{phot} varies with LET for low LET values. We have assumed a simple linear relation between a/a_{phot} and LET also for low LETs, but it is possible that a/a_{phot} approaches 1, or another value on the intercept, non-linearly with decreasing LET.

Upon a closer examination, it was the cell lines with low $(\alpha/\beta)_{\text{phot}}$ that contributed to the positive relation between a/a_{phot} and LET. The cell lines with $(\alpha/\beta)_{\text{phot}} \geq 15$ showed no statistically significant relation between a/a_{phot} and LET, i.e. the slope k was not significantly larger than zero. We have developed an

expression where the sensitivity to LET changes is linked to the a/β ratio of photons, Equation 2, so that a/a_{phot} increases with increasing LET with a slope that decreases with increasing $(a/\beta)_{\text{phot}}$. Statistical analyses supported these assumptions.

When it comes to the $\beta/\beta_{\text{phot}}$ ratio, no support for an LET dependence was found, and hence the assumption of a constant β equal to β for photons is reasonable. In conclusion, the assumptions made in the development of the RBE model were all supported by the experimental data used in this study.

The resulting RBE model fitted the experimental RBE values well ($r^2 = 0.76$), and significantly better compared to the standard constant RBE ($p\text{-value} < 0.01$). The proposed model predicts an increasing RBE with increasing LET in a cell dependent way: the a/β ratio of photons determines the strength of the positive relation between RBE and LET of protons. In other words, different cell lines differ in their sensitivity to LET changes which is determined by their a/β ratio of photons. So, clearer trends in the variation of RBE with LET are revealed by stratifying the data: for low $(a/\beta)_{\text{phot}}$ cell lines the highest RBE values are found and a distinct increase in RBE with LET is observed, whereas for high $(a/\beta)_{\text{phot}}$ the RBE is low and no LET dependence is found (see Figure 3). In fact, experimental RBE values lower than one are seen indicating that photon radiation might be more effective in cell killing than protons in this group of cells. Our results have the implication that late responding tissues (low $(a/\beta)_{\text{phot}} \approx 3$) are more sensitive to LET changes than early responding tissues and most tumors (high $(a/\beta)_{\text{phot}} \approx 10$). Moreover, in a treatment planning situation, caution in selecting an $(a/\beta)_{\text{phot}}$ ratio for a tissue is most important in the low range of $(a/\beta)_{\text{phot}}$ values since a small difference in this value gives a large change in the slope k (see Figure 2) and, ultimately, a large change in the RBE.

The tendency of a higher RBE for cells with low $(a/\beta)_{\text{phot}}$ is in agreement with the conclusions made by Gerweck and Kozin [4]. They summarized the results of published experimental data where the measurements of RBE were obtained for different spread-out Bragg peaks (SOBP). SOBP are used to obtain a homogeneous dose distribution throughout the tumor by modulating the proton energy. This means that the SOBP is composed of multiple superimposed Bragg peaks of different energies and, hence, there will be a spectrum of LETs in the SOBP. In this study, cell survival data obtained from unmodulated proton beams was chosen instead to have a well-defined LET in order to better identify relations between RBE, LET, and $(a/\beta)_{\text{phot}}$.

Our evaluation of the RBE model indicates that, not only the sensitivity of the RBE to LET variations,

but also its sensitivity to dose variations depends on the $(a/\beta)_{\text{phot}}$. The model shows an increasing RBE with decreasing dose as seen in Figure 5 where the effect is most pronounced at low $(a/\beta)_{\text{phot}}$ and high LETs. For high $(a/\beta)_{\text{phot}}$ only a small or no dose effect is seen. Paganetti et al. [3] have reviewed published RBE values of in vitro and in vivo systems in a SOBP and concluded that a statistically significant increase in RBE is found for low doses per fraction in both systems, but less pronounced in vivo. Of all the in vitro experiments they studied, only three did not show this trend. Interestingly, two of these cell lines, human colon carcinoma LS174T [19] and human squamous cell carcinoma SCC25 [20], had a high $(a/\beta)_{\text{phot}}$ (the ratio was infinite and 47.5, respectively) and would therefore not be expected to show this trend according to the RBE model presented here. In the third study, where Chinese hamster ovary cells with an $(a/\beta)_{\text{phot}}$ of 1.83 were used [21], an increasing RBE with decreasing dose was observed in the end of a 3-cm SOBP and in the middle of a 0.5-cm SOBP, but the opposite relation was found in the beginning of a 3-cm SOBP and in the initial plateau of the beam. Perhaps this could be explained by a low LET in the initial plateau and the beginning of a SOBP so that small RBE changes could not be distinguished.

All taken together, the highest RBE values are expected for cell lines and tissues with low $(a/\beta)_{\text{phot}}$ receiving high LET and low dose per fraction. This combination can be obtained, e.g. when the end of the proton range is located in late-responding normal tissue. This is not an unusual situation since tumors located in the immediate vicinity of organs at risk are often selected for proton radiotherapy, and high-weighted spots or the distal end of a SOBP are frequently situated at the distal edge of the tumor in order to obtain a homogeneous dose distribution. Also in the laterally peripheral parts of a beam this combination of high LET, low dose per fraction, and low $(a/\beta)_{\text{phot}}$ can be obtained. An increased RBE in normal tissue may, if not taken into account, result in a too high prescription dose selected and a higher biological effect than expected. For example, a late reacting tissue with $(a/\beta)_{\text{phot}} = 3$, situated immediately downstream of the target volume, receiving 1 Gy per fraction and 6 keV/ μm would obtain an RBE of 1.48 according to the RBE model.

Tumors often receive relatively high LET components in proton radiotherapy since Bragg peaks are placed inside the target volume. However, the biological effect of the increased LET depends on the $(a/\beta)_{\text{phot}}$ as seen in this study. For some slowly growing tumors that have low $(a/\beta)_{\text{phot}}$, such as prostate cancer, it might be a significant gain with this increased LET. However, most tumors have relatively

high $(\alpha/\beta)_{\text{phot}}$ values and, therefore, the increased LET might not result in a favorable increased RBE. RBE values even lower than 1.1 may be obtained when using a simultaneous integrated boost technique if the clinical target volume (CTV) surrounding the boosted gross tumor volume (GTV) receives dose mainly from the plateau region of the proton beam. A CTV with $(\alpha/\beta)_{\text{phot}} = 10$ receiving 2 Gy per fraction and 2 keV/ μm gives a predicted RBE value of 1.06. With the RBE model presented in this study the effects of different LET values, α/β values of photons, and doses can simultaneously be taken into account.

In this study, in vitro data have been used to evaluate the RBE model. Ideally, there should exist relevant in vivo data for human tissue where well-defined LETs were used, but these data are at present scarce. RBE variations are expected to be smaller for in vivo systems [3]. Until more data are available, in vitro data can be used to estimate the potential relative effects rather than absolute values.

After the completion of the study at hand, Carabe et al. [22] published an extension of the radiobiological model originally presented by Dale and Jones [14]. In their article they propose an expression similar to ours for the a/a_{phot} ratio (called RBE_{max} in their study). Their approach for parameter determination differs from the one used in this study in that they fit their model only to experimental data from V79 cells. From this data they extrapolate to other cell lines. The strength of our approach is that we fit to experimental data of a range of different $(\alpha/\beta)_{\text{phot}}$ ratios and LET values simultaneously, and that we use statistical model selection methods to empirically evaluate the form of our parametric function.

In conclusion, the sensitivity of cells to x-rays, characterized with the α/β ratio, is useful in estimating their sensitivity to proton radiation. By accounting for α/β ratio of photons, clearer trends between RBE and LET was revealed. The RBE was found to increase with increasing LET for cell lines with low $(\alpha/\beta)_{\text{phot}}$ ratio, whereas limited variability in RBE was observed at high ratios. The proposed RBE model accounts for an RBE that depends on dose, LET and α/β ratio of the reference radiation.

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Supplementary material available online

Appendix to be found online at <http://informahealthcare.com/doi/abs/10.3109/0284186X.2012.705892>