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Fast neutron relative biological effects and implications for charged particle therapy

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ABSTRACT. In two fast neutron data sets, comprising *in vitro* and *in vivo* experiments, an inverse relationship is found between the low-linear energy transfer (LET) α/β ratio and the maximum value of relative biological effect (RBE_{max}), while the minimum relative biological effect (RBE_{min}) is linearly related to the square root of the low-LET α/β ratio. RBE_{max} is the RBE at near zero dose and can be represented by the ratio of the α parameters at high- and low-LET radiation exposures. RBE_{min} is the RBE at very high dose and can be represented by the ratio of the square roots of the β parameters at high- and low-LET radiation exposures. In principle, it may be possible to use the low-LET α/β ratio to predict RBE_{max} and $RBE_{min,}$ providing that other LET-related parameters, which reflect intercept and slopes of these relationships, are used. These two limits of RBE determine the intermediate values of RBE at any dose per fraction; therefore, it is possible to find the RBE at any dose per fraction. Although these results are obtained from fast neutron experiments, there are implications for charged particle therapy using protons (when RBE is scaled downwards) and for heavier ion beams (where the magnitude of RBE is similar to that for fast neutrons). In the case of fast neutrons, late reacting normal tissue systems and very slow growing tumours, which have the smallest values of the low-LET α/β ratio, are predicted to have the highest RBE values at low fractional doses, but the lowest values of RBE at higher doses when they are compared with early reacting tissues and fast growing tumour systems that have the largest low-LET α/β ratios.

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The medical prescription of charged particle therapy, which always contains high-linear energy transfer (LET) in the Bragg peak region, is usually in the form of a biological equivalent dose, usually referred to as the gray equivalent. This is instead of a real physical dose as is used to prescribe standard megavoltage X-ray therapy. Conversion from physical to biological dose uses the relative biological effect (RBE) concept, so that the delivered high-LET dose is the physical dose of the low-LET radiation divided by the RBE. RBE is known to vary with dose per fraction, from a maximum value (RBE_{max}) at very low dose per fraction to a lower limiting value of RBE_{min} at very high dose per fraction. Previously, fixed RBE values were used to provide the biological equivalent dose at the prescription point or isodose surface, as in the case of fast neutron therapy where an RBE of 3 was too often assumed for all tissues at all fractional doses, but with the inevitable consequence of under or over dosage (relative to megavoltage X-rays) in other tissues where doses were higher or lower [1].

Dale et al [2] have pointed out the potentially serious errors that can occur when RBE values are not known with sufficient accuracy in high-LET radiations, such as in heavy charged particle beam therapy. The resultant biological dose may be under- or overestimated by an extent that far exceeds the normal requirement for physical dose accuracy in conventional X-ray based radiotherapy. Equations are available for isoeffective biological dose calculations, which use the low-LET α/β ratio, $(\alpha/\beta)_L$, along with RBE_{max} and RBE_{min} as dose multiplying factors. It is $(\alpha/\beta)_L$ that determines the fractionation sensitivity in specific tissues for all forms of radiotherapy, including high-LET radiotherapy (providing that these two RBE parameters are used).

The present article investigates the relationship between RBE_{max}, RBE_{min} and $(\alpha/\beta)_L$ for megavoltage X-rays and fast neutrons, the latter class of radiation as a radiobiological tool for the investigation of high-LET radiation effects.

Methods and materials

In vitro cell survival studies in 30 human cell lines exposed to 4 MeV X-rays (low-LET) and fast neutron (high-LET), using the Clatterbridge cyclotron, have been published by Warenius et al [3]. Although the entire data set is analysed, data censoring is used to eliminate extreme repair mutants and experimental data fitting

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Table 1. Data (point estimates) taken from Carabe-Fernandez et al [4] and used in this report

Assay	Low LET α/β	RBE_{max}	RBE_{min}
Oesophagus, LD_{50}	16.24	3.05	2.27
Bone marrow (haematocrit)	1.15	26.33	1.19
Kidney (EDTA)	1.22	20.58	1.35
Kidney	2.23	15.85	0.73
Mouse skin	17.42	5.35	0.41
Colorectal, LD_{50} (2 months)	28.96	5.70	1.46
Colorectal, LD_{50} (15 months)	3.11	12.56	0.41
Lung (28 weeks)	2.93	7.63	0.58
Lung LD_{50} (28 weeks)	5.95	5.19	0.99
Lung LD_{50} (68 weeks)	2.32	8.62	0.72
Pig skin (acute)	15.17	3.46	0.71
Pig skin (late)	5.25	4.26	0.91

EDTA, ethylenediaminetetraacetic acid; LD_{50}, lethal dose for 50%; LET, linear energy transfer; RBE_{max}, maximum value of relative biological effect; RBE_{min}, minimum value of relative biological effect.

uncertainties [where $(\alpha/\beta)_L$ is >50 Gy and if high-LET β-parameters are $\leqslant 0.01\,Gy^{-2}$ and where RBE_{min} is <0.2]. This leads to omission of six data points that possess these criteria.

The *in vivo* experimental data set, which used X-rays and fast neutrons in various normal tissue types, provides values of low-LET α/β, RBE_{min} and RBE_{max} published by Carabe-Fernandez et al [4] (in their Table 1), although these data do not include standard error estimates. Some experimental results were censored, *e.g.* if the biological end point is unlikely to reflect a satisfactory clonogenic end point and where further data on the same animals represent a longer temporal data set more representative of late tissue damage. Experiments that are sixth, seventh and eighth (colorectal damage reflected by body weight at various time points) in Table 1 of Carabe-Fernandez et al [4] are censored as they represent a potentially inappropriate surrogate for colorectal damage; the final, and most relevant, pathological late effect reported by Terry et al [5] is included. Also, one data point with RBE_{min} of 0.1 has been excluded in the RBE_{min} *in vivo* analysis, as this is likely to represent experimental error. In summary, the data adapted from Carabe-Fernandez et al [4] are given in Table 1 of this review.

Least squares fitting and non-linear regression are used to analyse the above data using Mathematica (Wolfram, Champaign, IL) software, with and without the use of standard error corrections and non-linear fit programmes.

The analysis is based on the linear quadratic model of radiation effect, with special attention to the inclusion of RBE_{min} and RBE_{max} concepts for high-LET radiations [4, 6]. The symbols used are shown in Table 2.

The low-LET radiation biological effective dose (BED) is expressed as:

$$N_L d_L \left(1+\frac{d_L}{(\alpha/\beta)_L}\right)$$

and the high-LET BED as:

$$N_H d_H \left(RBE_{max}+\frac{RBE_{min}{}^2 d_H}{(\alpha/\beta)_L}\right)$$

The mathematical forms of the derivations and fitted relationships are given in Appendix A. The equations used in Appendix B are used to obtain the graphical displays of estimated RBE with dose per fraction. The calculation method to obtain the dose at which RBE is equal (at cross-over points) for two different tissues or tumours, each with different α/β ratios, is given in Appendix C.

Results

In vitro *data*

The relationship between $(\alpha/\beta)_L$ and RBE_{min} [shown as $RBE_{min}=S\times\sqrt{(\alpha/\beta)_L}$ in Equation 7 in Appendix A] is clearly seen in the data points displayed in Figure 1 for the entire data set of 30 cell lines. There is a good overall statistical fit for the equations $0.31\sqrt{(\alpha/\beta)_L}$ and

Table 2. Symbols used in text and appendices

Symbol (and units)	Meaning
LET ($keV\,\mu M^{-1}$)	Linear energy transfer (LET) is the average loss of energy per micrometre length of track
d_L (Gy)	Dose per fraction of low-LET radiation
d_H (Gy)	Dose per fraction of high-LET radiation
N_L	Number of low-LET fractions
N_H	Number of high-LET fractions
α_L (Gy^{-1})	Low-LET radiosensitivity per unit dose
α_H (Gy^{-1})	High-LET radiosensitivity per unit dose
β_L	Low-LET radiosensitivity per unit dose squared
β_H	High-LET radiosensitivity per unit dose squared
$(\alpha/\beta)_L$	The ratio of α/β for low-LET radiation
RBE	The ratio of low-LET dose divided by high-LET dose for a specific biological end point. Relative biological effect (RBE) varies with dose and can take any value between the limits of RBE_{max} at near zero dose to RBE_{min} at very high dose
RBE_{max}	The ratio of α_H/α_L and is the RBE at near zero dose
RBE_{min}	The ratio of $\sqrt{(\beta_H/\beta_L)}$ and is the RBE at very high dose
C	The minimum value of RBE_{max} when low-LET α/β is smallest owing to biological constraints
A	Coefficient controlling change of RBE_{max} with increasing values of low-LET α/β
K	The lowest value of RBE_{min} when low-LET α/β is smallest owing to biological constraints
B	Coefficient controlling change of RBE_{min} with increasing values of low-LET α/β
Q	Coefficient controlling relationship between RBE_{max} and low-LET α/β if no boundary conditions
S	Coefficient controlling relationship between RBE_{min} and low-LET α/β if no boundary conditions

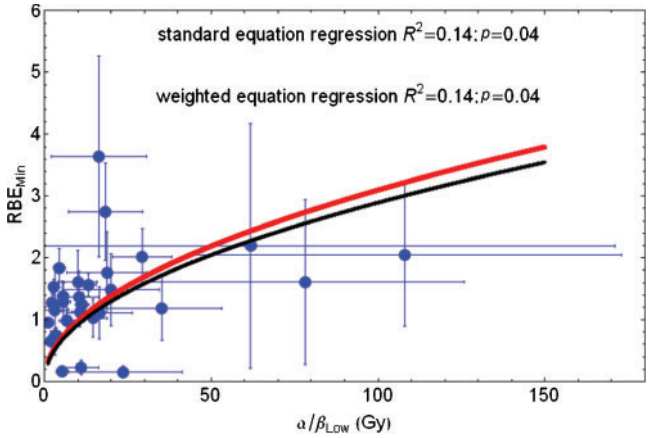

Figure 1. Plot of RBE_{min} with increasing low-LET α/β ratio for the entire *in vitro* data set and fitted using Equation 7 in Appendix A. Red line, standard regression; black line, error weighted regression; RBE_{min}, minimum value of relative biological effect; LET, linear energy transfer.

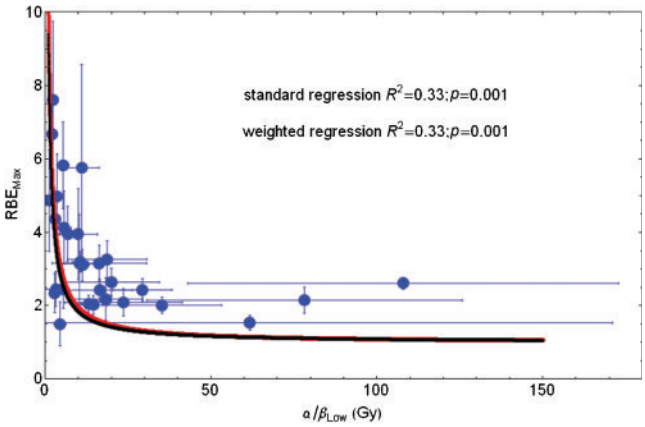

Figure 3. Plot of RBE_{max} with increasing low-LET α/β ratio for entire *in vitro* data set and fitted using Equation 6 in Appendix A. Red line, standard regression; black line, error weighted regression; RBE_{max}, maximum value of relative biological effect; LET, linear energy transfer.

$0.29\sqrt{(\alpha/\beta)_L}$ using uncorrected and standard error corrected least squares fits, respectively. Using non-linear regression, without standard error correction, the estimated mean and 95% confidence interval for S are 0.31 (0.23–0.38).

If the three lowermost RBE_{min} values are censored, the resulting fit is only slightly different [$RBE_{min}=0.33\sqrt{(\alpha/\beta)_L}$]. When Equation 11 (Appendix A) is used, better fits are obtained, as shown in Figure 2, where $RBE_{min}=0.76+0.22\sqrt{(\alpha/\beta)_L}$ by fitting the (mean) data points or $RBE_{min}=0.72+0.18\sqrt{(\alpha/\beta)_L}$; if standard error corrections are also used, the 95% confidence interval for the two respective numerical parameters are 0.09–1.42 and 0.02–0.42 for the former equation. These equations provide realistic values of RBE_{min} that are not too small for small low-LET α/β values and are reasonably close to unity.

Figure 3 shows the reciprocal relationship between RBE_{max} and low-LET α/β for all data points, with curves fitted using the simple reciprocal equations as in Equation 6 (Appendix A). Both the uncorrected data [$RBE_{max}=12.40/(\alpha/\beta)_L$] and standard error corrected data [$RBE_{max}=11.04/(\alpha/\beta)_L$] fits are poor at high α/β values, with some estimates of RBE_{max} below unity for large α/β. The 95% confidence interval for the 12.4 estimate is 8.85–15.9.

If the data are censored by removing inappropriate α/β values in repair mutants, as discussed by Jones [6], and the phase plane changed by adopting Equation 10 (Appendix A) then improved fitting is obtained, as shown in Figure 4. The fitted equations are then $RBE_{max}=2.43+4.97/(\alpha/\beta)_L$ and $RBE_{max}=2.29+4.81/(\alpha/\beta)_L$ for using uncorrected point estimates and the standard error corrected least squares fitting methods, respectively. Both methods give the same degree of statistical significance when estimated by non-linear regression fitting. The 95% confidence intervals for the numerical parameters are 1.67–3.2 and 2.15–7.79 in the first case.

In vivo *data*

The results are shown for RBE_{min} and RBE_{max} in Figures 5 and 6, respectively. The derived

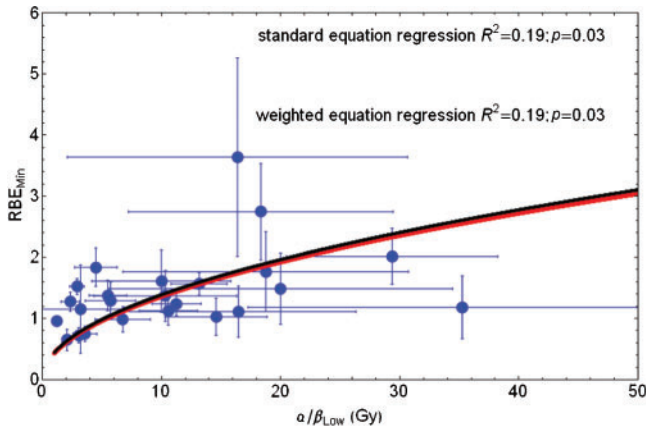

Figure 2. Plot of RBE_{min} with increasing low-LET α/β ratio for the censored *in vitro* data set and fitted using Equation 11 in Appendix A. Red line, standard regression; black line, error weighted regression; RBE_{min}, minimum value of relative biological effect; LET, linear energy transfer.

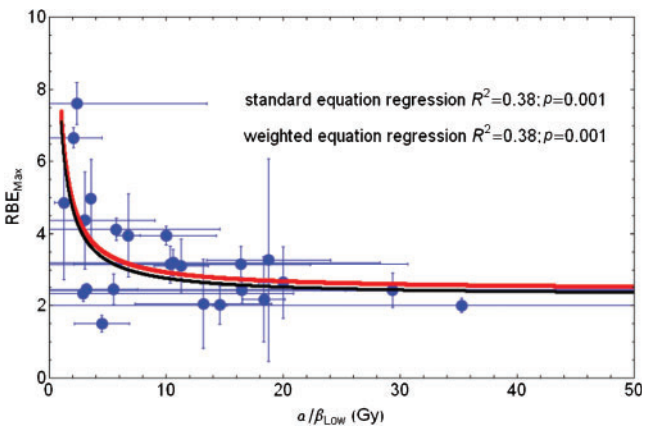

Figure 4. Plot of RBE_{max} with increasing low-LET α/β ratio for entire *in vitro* data set and fitted using Equation 9 in Appendix A. Red line, standard regression; black line, error weighted regression; RBE_{max}, maximum value of relative biological effect; LET, linear energy transfer.

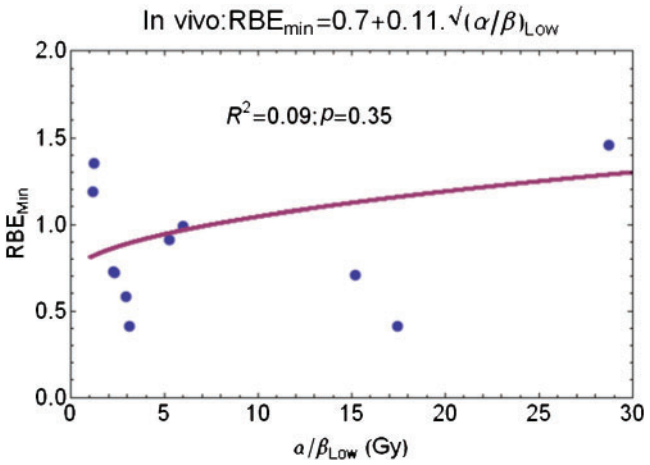

Figure 5. Plot of RBE_{min} with increasing low-LET α/β ratio for censored *in vivo* data set and fitted using Equation 11 in Appendix A. RBE_{min}, minimum value of relative biological effect; LET, linear energy transfer.

$RBE_{min}=0.7+0.11\sqrt{(\alpha/\beta)_L}$ fit is statistically insignificant, with numerical parameter 95% confidence intervals of −0.03 to 1.42 and −0.14 to 0.36, respectively. The poor statistical fit is probably due to the inherent difficulties associated with measuring the very low β parameter *in vivo* because of bio-heterogeneity, as well the reasons discussed elsewhere [6], *i.e.* the large numbers of animals required to provide higher levels of statistical confidence.

In contrast, the RBE_{max} equation fitting results are better, they have a clearly defined reciprocal relationship and significant statistics (Figure 6). The non-linear fit to Equation 10 in Appendix A gives $RBE_{max}=2.07+24.59/(\alpha/\beta)_L$, and where the 95% confidence intervals on the two numerical parameters are 0.5–4.65 and 18.45–30.72, respectively.

Figure 7 shows the effect of changing neutron dose per fraction on RBE, using Equation 3 (Appendix B), assuming from the above results that $RBE_{max}=2.1+24.59/(\alpha/\beta)_L$ and $RBE_{min}=0.76+0.22\sqrt{(\alpha/\beta)_L}$.

It is evident that the curves with the lowest $(\alpha/\beta)_L$ ratios extend to higher RBE_{max} values at very low doses and have the lowest RBEs at high doses. The cell systems

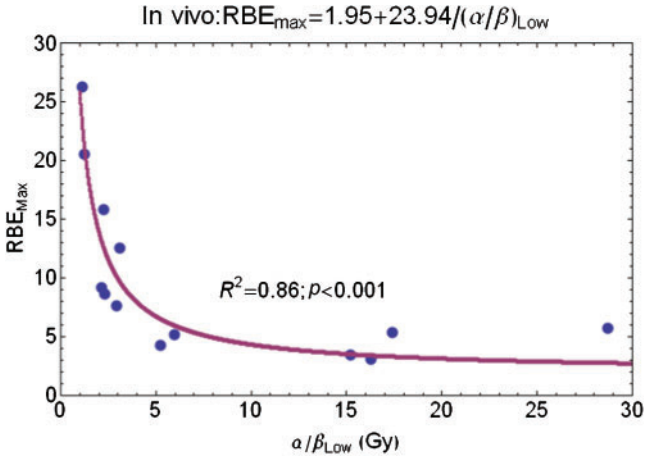

Figure 6. Plot of RBE_{min} with increasing low-LET α/β ratio for entire *in vivo* data set and fitted using Equation 10 in Appendix A. RBE_{min}, minimum value of relative biological effect; LET, linear energy transfer.

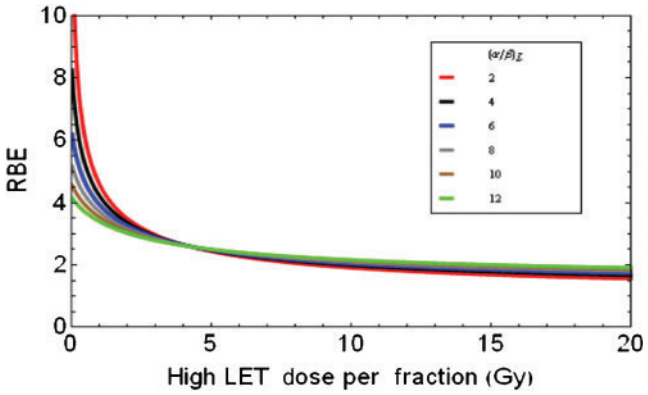

Figure 7. Relationships between high-LET dose per fraction and RBE for variable low LET α/β ratios which are used to partly determine the RBE_{max} (the intercept value of RBE at zero dose) and RBE_{min} (the asymptotic RBE at very high dose). RBE, relative biological effect; LET, linear energy transfer.

with the highest $(\alpha/\beta)_L$ ratios are predicted to show little change in RBE with dose per fraction, while also having the highest RBEs at large fractional doses.

Figure 8 shows an attempt to scale down the neutron RBEs to those more appropriate for protons and where there is little change in RBE with dose per fraction for tissues or tumour systems with higher $(\alpha/\beta)_L$ values. For this to be achieved, the RBE_{max} is assumed to be $1.05+1/(\alpha/\beta)_L$ and the RBE_{min} is 1.05.

Discussion

The UK research councils and cancer charities have invested considerable resources in experimental neutron radiobiology and clinical applications. Harold Gray thought that neutrons were a good tool for investigating high-LET effects, but did not think them appropriate for radiotherapy [Dr OCA Scott, London, UK, 2002, personal communication]. Neutrons proved to be disappointing in randomised clinical trials, for reasons that are now better

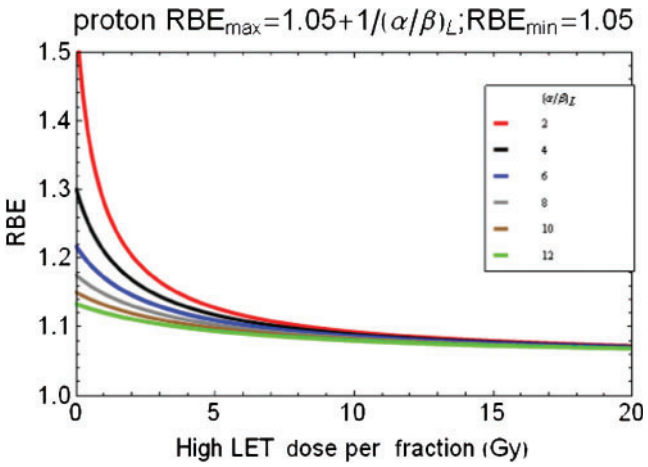

Figure 8. Scaled data from Figure 7 for speculation of proton relative biological effect (RBE) changes with dose per fraction by reduction of RBE_{max} using lower parameters as shown above graphic. RBE_{max}, maximum value of relative biological effect.

understood [1, 7]. It is important that the wealth of experimental data sets produced by British scientists should be analysed as completely as possible and with special attention to any general principles that might guide future research in charged particle therapy.

The data plots and analysis have shown a statistically significant inverse relationship between RBE_{max} and low-LET α/β and a linear relationship between RBE_{min} and the square root of α/β. These findings allow the possibility for tentatively deriving RBE_{max} and RBE_{min} values from low-LET α/β ratios, which are increasingly being identified for normal tissues and a variety of tumours. Variable RBE values can then be obtained for changes in dose per fraction, which occur in three-dimensional treatment dose distribution plans, or when prescribed dose is changed. Such possibilities can of course apply only to radiation treatment modalities with LET equivalent to the fast neutrons used in the data presented here.

The model presented in Appendix A is based on the premise that a change from low- to high-LET is accompanied by an immediate change in RBE_{max}, which can be further increased by a change in the more fundamental low-LET α/β ratio. The results obtained suggest that RBE values at low dose will be highest in tissues with very low α/β values, including those found in many slow growing tumours and late reacting normal tissues, such as brain and spinal tissues in which some of the most serious side effects of radiotherapy occur; at high doses the highest RBE will be found for tumours and tissues with high α/β ratios. Since tumours with low proliferation indices (and consequently low α/β ratios) are predicted to have higher RBE values, the predictions made are consistent with the data of Batterman et al [8] in which human tumours with longer volume doubling times have the highest RBE values. The findings in the current paper are consistent with the normal toxicity results in the British neutron trials in which the neutron dose per fraction at Edinburgh was reduced to 0.5 Gy per fraction rather than approximately 1.4 Gy [1, 7] at Hammersmith and Clatterbridge (the equivalent megavoltage low-LET X-ray doses would be 1.5 and 4.2 Gy for an RBE of 3; and 1.25 and 3.5 Gy for an RBE of 2.5. The normal tissue toxicity was arguably worse at Edinburgh, although there were other important factors, such as beam energy and number of fields used. As seen in Figure 8, a reduction on neutron dose per fraction would allow a greater spread in RBE values with exacerbation of late effects associated with low α/β ratio tissues such as central nervous system (CNS) and late fibrosis.

The method presented has provided a good statistical fit for two quite different data sets (with the exception of RBE_{min} *in vivo*), but there are differences in the parameter values obtained. These differences may be partly LET dependent and, as a result of the different neutron energies (and spectra) used, the lower energy Hammersmith beam [d(15)+Be] produces a higher RBE than the Clatterbridge beam (62.5 MeV+Be). Additionally, the range of doses used would be limited to those necessary to produce toxic events, so that measurement of the true RBE_{min} at much higher doses would not be feasible. The conditions of the experiments have a marked difference, *i.e. in vitro* cells are grown in optimum conditions (with respect to nutrients and oxygenation) and irradiated in logarithmic growth conditions, which may truncate repair and not allow repair classes that operate over longer time courses. Potentially lethal damage (PLD) repair is curtailed in *in vitro* systems. In contrast, *in vivo* irradiations involve many different target cells and full PLD repair in studies of normal tissue effects. Thus, different values of radiosensitivities are to be expected in the two classes of data.

The findings presented in the current paper are independent of microdosimetry considerations, although such a framework that includes a similar assumption about RBE_{max} linked to α/β ratio was used by Hawkins [9, 10], but in the form of $1+\gamma/(\alpha/\beta)_L$, where γ is a LET dependent parameter and is broadly similar to Equation 10 in Appendix A. Paganetti et al [11] reached a similar conclusion by using Monte-Carlo particle track simulations.

The separate local effect model used in Germany [12] also presumes a relationship with low-LET α/β values, but also takes further assumptions based on nuclear volume and a linear shape of the cell survival curve at high doses, which have been found to be poorly predictive in some experiments [13]. The local effect model is undergoing further modification at the present time. From the data presented in the current paper, it is not surprising that it will be difficult to detect a clear relationship between RBE and α/β—at say surviving fractions of 0.1 or 0.01—since the RBE will, at some low doses, be more related to the inverse of α/β and at high doses more directly proportional to α/β.

Better knowledge of RBE_{max} and RBE_{min} values would allow dose per fraction to be adjusted over a wide range of doses, which would be applicable for fractionated and hypofractionated treatments. This is in marked contrast to the existing models including that used in Japan for carbon ion therapy [14]. In principle it should be possible to use representative low-LET α/β values to predict RBE to a reasonable degree of accuracy at any dose level. More work on determination of the parameters given in the appendices, that is Q, S or the better alternatives C, K, A and B, is urgently indicated for all forms of particle therapy.

The method used is dependent on the validity of the linear quadratic model of radiation effect and all the assumptions made. The data were found from *in vitro* experiments using fast neutrons of maximum energy 64 MeV, whereas the animal data were obtained using 24 MeV neutrons, which will influence the RBE values. A more comprehensive system for adjusting RBE in relation to LET is required, but the present results are sufficient to show the general principles. Statistical fitting is mostly good, despite the inevitable large biological variation, the different experimental conditions and beam qualities used in the different experimental groups.

The scaling down of RBE parameters to likely values for proton therapy is especially tentative, but provides an important insight into the continuing debate as to whether the RBE is 1.1 in all tissues and at all doses. This policy was used in Boston and was subsequently adopted in most proton therapy centres (with the possible sole exception of Tzukuba where no correction was used). The experimental data at Boston, which were used to justify the choice of an RBE of 1.1, have been summarised by Pagannetti et al [15, 16]. Close

examination of their results shows that their *in vitro* data contain mainly fast growing Chinese hamster ovary cells and their *in vivo* data predominately of acute reacting assays. Both systems will have low fractionation sensitivity and high α/β ratios, and, according to our current hypothesis, will not show a marked change in RBE with dose per fraction. It is also apparent that the American National Institutes of Health did not fund Boston with a grant to test RBE in brain tissue [Dr H Suit, Heidelberg, Germany, 2009, personal communication], in which the α/β ratio is known to be approximately 2 Gy in most systems and where we might expect the RBE to exceed 1.1 at low doses per fraction. It is vital that more proton therapy radiobiology should be done to resolve this issue, and improve the safety of proton and heavy ion treatment especially within the CNS.

Further work is necessary to validate the fast neutron findings for a range of charged particle radiations (*e.g.* protons, deuterons, helium, neon or carbon) at varying energies and with mixtures of low- and high-LET, as will be found by spreading the Bragg peaks during charged particle therapy. The carbon ions pioneered in Japan have RBE values in the spread out Bragg peak close to those of fast neutrons with LET of around 85 KeVμM^{-1} [15], and the general trends found in the current paper are consistent with the *in vitro* carbon ion data published by Suzuki et al [17].

The model presented can, in principle, act as a hypothesis for direct testing in experiments designed to confirm or disprove these findings. Such work is vital to extend the application of ion beam therapies for cancer [18–21]. Ideally, a wide range of experiments should be performed to determine the parameters that link $(\alpha/\beta)_L$ to RBE at the various mixtures of LET values obtained with each particle therapy beam, and to find how these relate to the average LET at volume element in the treatment planning process.

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Appendix A

Symbols used are summarised in Table 2. It has previously been shown that RBE_{max} and RBE_{min} act as multipliers of the low-LET α and β parameters. Application of limit theory [3, 4, 17] shows how these parameters have the following identities (note that the subscripts L and H refer to low- and high-LET radiations respectively):

$$\mathrm{RBE}_{\max} = \frac{\alpha_{\mathrm{H}}}{\alpha_{\mathrm{L}}} \tag{A1}$$

so that

$$\alpha_L = \frac{\alpha_H}{\mathrm{RBE}_{\max}} \tag{A2}$$

and

$$\mathrm{RBE_{min}}^2 = \frac{\beta_\mathrm{H}}{\beta_\mathrm{L}} \tag{A3}$$

so that

$$\beta_L = \frac{\beta_H}{\mathrm{RBE_{min}}^2} \tag{A4}$$

It follows, by dividing Equation A2 by Equation A4, that

$$\frac{\alpha_L}{\beta_L} = \frac{\alpha_H}{\beta_H} \times \frac{\mathrm{RBE_{min}}^2}{\mathrm{RBE_{max}}} \tag{A5}$$

Rearrangements of this last equation allow $\mathrm{RBE_{max}}$ and $\mathrm{RBE_{min}}$ to be expressed as:

$$RBE_{\max} = \frac{\alpha_H}{\beta_H} \times \frac{\mathrm{RBE_{min}}^2}{\left(\frac{\alpha_L}{\beta_L}\right)} = \frac{Q}{\left(\frac{\alpha_L}{\beta_L}\right)} \tag{A6}$$

and

$$\mathrm{RBE_{min}} = \sqrt{\frac{\alpha_\mathrm{L}}{\beta_\mathrm{L}}} \times \frac{\mathrm{RBE_{max}}}{\frac{\alpha_H}{\beta_H}} = S\sqrt{\frac{\alpha_L}{\beta_L}} \tag{A7}$$

where the replacements Q and S are

$$\mathrm{Q} = \frac{\alpha_\mathrm{H}}{\beta_\mathrm{H}} \times \mathrm{RBE_{min}}^2 \tag{A8}$$

and

$$\mathrm{S} = \sqrt{\frac{\mathrm{RBE_{max}}}{\frac{\alpha_H}{\beta_H}}} \tag{A9}$$

Here Q and S are treated as constants which represent the average value of their component parameters in the populations studied.

However, the relevant physics and biology imposes limits on the ranges of these parameters, for example $\mathrm{R_{max}}$ values <2 are not to be expected in fast neutrons, and $\mathrm{RBE_{min}}$ values close to 0 cannot occur. The domains (or phase plane) of the functions must be corrected so that values in unallowed regions cannot occur. Consequently, Equations A6 and A7 are modified by imposing a lower boundary condition, while preserving the reciprocal and direct square functions, respectively:

$$\mathrm{RBE_{max}} = C + \frac{A}{\left(\frac{\alpha_L}{\beta_L}\right)} \tag{A10}$$

and

$$\mathrm{RBE_{min}} = K + B\sqrt{\frac{\alpha_L}{\beta_L}} \tag{A11}$$

Where C is the minimum possible value of $\mathrm{RBE_{max}}$ and K is the minimum possible value of $\mathrm{RBE_{min}}$ for a particular quality of radiation and A and B are coefficients that determine the slope of the change in $\mathrm{RBE_{max}}$ and $\mathrm{RBE_{min}}$, respectively. These additional parameters on the right-hand side of Equations A10 and A11 can be estimated from the data sets.

Appendix B

Variable RBE values are found by solving for $\mathrm{d_L}$ in the isoeffective BED relationship:

Low-LET bioeffective dose = high-LET bioeffective dose which is represented by:

$$\mathrm{N_L d_L}\left(1+\frac{d_L}{(\alpha/\beta)_L}\right) = \mathrm{N_H d_H}\left(\mathrm{RBE_{max}} + \frac{\mathrm{RBE_{min}}^2 d_H}{(\alpha/\beta)_L}\right) \tag{A12}$$

The variable RBE is then obtained by dividing by d_H so that:

$$\mathrm{RBE} = \frac{0.5}{d_H}\left(-\left(\frac{\alpha}{\beta}\right)_L + \sqrt{\left(\frac{\alpha}{\beta}\right)_L^2 + 4d_H\left(\frac{\alpha}{\beta}\right)_L \mathrm{RBE_{max}} + 4{d_H}^2 \mathrm{RBE_{min}}}\right) \tag{A13}$$

It then follows that $\mathrm{RBE_{max}}$ and $\mathrm{RBE_{min}}$ can be replaced by the equations in Appendix A (Equations A10 and A11) to give:

$$\mathrm{RBE} = \frac{0.5}{d}\left(\left(\frac{\alpha}{\beta}\right)_\mathrm{L} + \sqrt{\left(\frac{\alpha}{\beta}\right)_L^2 + 4d_H\left(\frac{\alpha}{\beta}\right)_L\left(C + \frac{A}{\left(\frac{\alpha}{\beta}\right)_L}\right) + 4{d_H}^2 \times \left(K + B\sqrt{\left(\frac{\alpha}{\beta}\right)_L}\right)}\right) \tag{A14}$$

RBE can then be plotted against low-LET α/β.

Appendix C

Position of cross-over points of RBE with dose per fraction.

Here the RBEs will be equal for all $(\alpha/\beta)_\mathrm{L}$ values, for which, to simplify the equations, the symbol k is used

instead of α/β, with k_1 and k_2 representing two different low-LET α/β ratios:

$$\frac{0.5}{d_H}\left(-k_1+\sqrt{{k_1}^2+4d_Hk_1\left(C+\frac{A}{k_1}\right)+4{d_H}^2(K+Bk_1)}\right)$$
$$=\frac{0.5}{d_H}\left(-k_2+\sqrt{{k_2}^2+4d_Hk_2\left(C+\frac{A}{k_2}\right)+4{d_H}^2(K+Bk_2)}\right)$$

So that:

$$-k_1+\sqrt{{k_1}^2+4d_Hk_1\left(C+\frac{A}{k_1}\right)+4{d_H}^2(K+Bk_1)}$$
$$=-k_2+\sqrt{{k_2}^2+4d_Hk_2\left(C+\frac{A}{k_2}\right)+4{d_H}^2(K+Bk_2)}$$

from which a solution can be obtained for d_H. This is best calculated using computer software as the equation for the solution is rather long.

There is a unique solution for the cross-over points for each pair of α/β ratios.