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## The incorporation of the concept of minimum RBE ( $RBE_{\min}$ ) into the linear-quadratic model and the potential for improved radiobiological analysis of high-LET treatments

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### Abstract

**Purpose:** The formulation of relative biological effectiveness (RBE) for high linear energy transfer (high-LET) radiation treatments is revisited. The effects of changed production of sub-lethal damage with varying LET is now considered via the  $RBE_{\min}$  concept, where  $RBE_{\min}$  represents the lower limit to which RBE tends at high doses per fraction.

**Materials and methods:** An existing linear-quadratic formulation for calculating RBE variations with fractional dose for high-LET radiations is modified to incorporate the twin concepts of  $RBE_{\max}$  (which represents the value of RBE at an effective dose-per-fraction of 0 Gy) and  $RBE_{\min}$ .

**Results:** Fits of the model to data showed  $RBE_{\min}$  values in the range of 0.1–2.27. In all cases the raw data was a better statistical fit to the model which included  $RBE_{\min}$ , although this was only very highly significant in one case. In the case of the mouse oesophagus it is shown that, if change in the  $\beta$ -radiosensitivity coefficient with LET is considered as trivial, an underestimation > 5% in RBE can be expected at X-ray doses of 2 Gy/fraction if  $RBE_{\min}$  is not considered. To ensure that the results were not biased by the statistical method used to obtain the parameter values relevant to this analysis (i.e., using fraction-size effect or Fe-plots), an alternative method was used which provided very similar correlation with the data.

**Conclusions:** If the production of sublethal damage is considered independent of LET, there will be a risk that non-corrected evaluation of RBE will lead to an over- or under-estimate of RBE at low doses per fractions (the clinically relevant region).

**Keywords:** High-LET radiotherapy, RBE, isoeffective fractionation schedules, acute and late reacting tissue, neutrons

### Introduction

The theory of dual radiation action (TDRA) (Kellerer & Rossi 1972) predicts that high linear energy transfer (high-LET) radiation increases the linear ( $\alpha$ ) component of radiation damage, while the quadratic ( $\beta$ ) component remains unchanged. As a consequence it is to be expected that, as fractional dose size decreases, the relative biological effectiveness (RBE) tends asymptotically to an intrinsic maximum value and which is the ratio of the initial slopes at zero dose of the associated cell-survival curves relating to the high-LET radiation in question and the reference (low-LET) radiation (Dale & Jones 1999). Similarly, the TDRA prediction of  $\beta$  being independent of radiation quality will mean that RBE tends to unity at very high doses.

However, this latter point has been found not to be the case for a number of systems and radiation qualities.

The analysis of experimental data (especially that relating to ultrasoft X-rays) using the TDRA model has shown that the assumption that  $\beta$  is constant can lead to very unsatisfactory prediction of biological effectiveness (Goodhead 1977). The conclusion is that the initial hypothesis of the TDRA is not valid and also that  $\beta$  should change as a function of LET, i.e.,  $\beta_H \neq \beta_L$ . Alternative mechanistic models have been proposed which allow for the variability of  $\beta$  on the basis of a LET-dependant saturable sub-lethal damage repair process.

This article presents an extension of an earlier radiobiological model developed by this group (Dale & Jones 1999) and introduces a new concept

( $RBE_{\min}$ ) within the linear-quadratic (LQ) model, which is defined as:

$$RBE_{\min} = \sqrt{\frac{\beta_H}{\beta_L}} \quad (1)$$

An experimental method is also proposed to search for the existence of the  $RBE_{\min}$  parameter which, together with  $RBE_{\max}$ , should provide a better description of the overall shape of the curve of RBE versus dose.

## Methods and materials

### *RBE and fractionated irradiation*

Under the LQ formulation, a given high-LET fraction dose ( $d_H$ ) will produce the same effect as a given low-LET dose ( $d_L$ ) only if:

$$\alpha_L d_L + \beta_L d_L^2 = \alpha_H d_H + \beta_H d_H^2 \quad (2)$$

But, taking into account that  $\alpha_H = \alpha_L RBE_{\max}$  and  $\beta_H = \beta_L RBE_{\min}^2$  (the latter being the new assumption), and dividing both sides of the resultant equation by  $\beta_L$ , we arrive at:

$$\begin{aligned} (\alpha/\beta)_L d_L + d_L^2 \\ = (\alpha/\beta)_L RBE_{\max} d_H + RBE_{\min}^2 d_H^2 \end{aligned} \quad (3)$$

Dividing both sides of Equation 3 by  $d_H$ , and noting that  $d_H = (d_L/RBE)$ , Equation 3 can be re-written purely in terms of low-LET parameters, as follows:

$$\begin{aligned} (\alpha/\beta)_L RBE + RBE d_L \\ = (\alpha/\beta)_L RBE_{\max} + RBE_{\min}^2 \frac{d_L}{RBE} \end{aligned} \quad (4)$$

Solving Equation 4 for positive values of RBE:

$$RBE = \frac{(\alpha/\beta)_L RBE_{\max} + \sqrt{(\alpha/\beta)_L^2 RBE_{\max}^2 + 4d_L RBE_{\min}^2 ((\alpha/\beta)_L + d_L)}}{2((\alpha/\beta)_L + d_L)} \quad (5)$$

Equation 5 describes RBE as a function of changing low-LET dose per fraction and is similar in form to an earlier equation (Dale & Jones 1999) but which did not allow for non-constancy of  $\beta$  with changing LET and therefore did not include the  $RBE_{\min}$  factor in the final term, i.e.,

$$RBE = \frac{(\alpha/\beta)_L RBE_{\max} + \sqrt{(\alpha/\beta)_L^2 RBE_{\max}^2 + 4d_L ((\alpha/\beta)_L + d_L)}}{2((\alpha/\beta)_L + d_L)} \quad (6)$$

This previous version was conceived as being adequate for low doses per fraction (or high surviving fraction) since  $\beta$  mediated damage is then relatively small compared with  $\alpha$  mediated damage. One relevant point of Equation 5 is that RBE is entirely determined by low-LET parameters,  $(\alpha/\beta)_L$  and  $d_L$  which, for a range of tissues, are more extensively tabulated. In Equation 5, as  $d_L \rightarrow 0$  Gy,  $RBE \rightarrow RBE_{\max}$ , which is also the case for the earlier formulation. However, as  $d_L \rightarrow \infty$  Gy,  $RBE \rightarrow RBE_{\min}$ , rather than unity.

### *Modification of BED equations to allow for RBE effects and calculation of relevant parameters*

$RBE_{\max}$  and  $RBE_{\min}$  are respectively the ratios of  $\alpha$  and  $\sqrt{\beta}$  as normally measured directly from survival curves. The measurement of these parameters is relatively easier in *in-vitro* experiments but, even then, the determination of both parameters from simple regression analysis applied to survival data is error prone. The only parameters used when specifying a patient treatment are the total dose and the dose per fraction, generally chosen to achieve the highest tumour control probability (TCP) while keeping the normal tissue complication probability (NTCP) as low as possible. Generic values of  $(\alpha/\beta)$  ratios for each individual tissue included in the treatment field can usually be assumed. The question then would be if there is any way of obtaining  $RBE_{\max}$  and  $RBE_{\min}$  values from the parameters commonly used clinically, i.e., number of fractions (n), total dose (TD) and  $(\alpha/\beta)$  ratios for the irradiated tissues.

These three parameters are related together by the Biologically Effective Dose (BED) concept. BED is defined as the theoretical total physical dose required for a given biological effect with a fractionated regime consisting of an infinite number of fractions of infinitesimally small doses and in the absence of repopulation. For low-LET radiations, the BED is formulated as (Joiner & Bentzen 2002):

$$BED_L = \frac{E_L}{\alpha_L} = n_L d_L \left( 1 + \frac{d_L}{(\alpha/\beta)_L} \right) \quad (7)$$

For high-LET radiations the “ $1 + \dots$ ” term is simply changed to “ $RBE_{\max} + \dots$ ” (Dale & Jones 1999), i.e.,

$$BED_H = n_H d_H \left( RBE_{\max} + \frac{d_H}{(\alpha/\beta)_L} \right) \quad (8)$$

Equations 7 and 8 may be derived from the respective equations which define “effect” (E) in a fractionated treatment. Taking that same methodology a

stage further and incorporating Equation 1 leads to the following sequence:

$$\begin{aligned}
 n_L(\alpha_L d_L + \beta_L d_L^2) &= n_H(\alpha_H d_H + \beta_H d_H^2) \\
 \Rightarrow n_L d_L \left(1 + \frac{d_L}{(\alpha/\beta)_L}\right) &= \\
 &= n_H \left(RBE_{max} d_H + \left(\frac{\beta_H}{\alpha_L}\right) d_H^2\right) \\
 &= n_H \left(RBE_{max} d_H + \left(\frac{\beta_L RBE_{min}^2}{\alpha_L}\right) d_H^2\right) \\
 &= n_H \left(RBE_{max} d_H + RBE_{min}^2 \frac{d_H^2}{(\alpha/\beta)_L}\right) \quad (9)
 \end{aligned}$$

This identity indicates that the BED for high-LET radiations [earlier written as Equation 8] should be more comprehensively defined as:

$$BED_H = n_H d_H \left(RBE_{max} + RBE_{min}^2 \frac{d_H}{(\alpha/\beta)_L}\right) \quad (10)$$

Equation 10 provides a tool with which to compare treatments carried out using radiations of different quality. The fact that Equation 10 has been formulated in terms of  $(\alpha/\beta)_L$  is convenient as this means the low- and high-LET BEDs are each being expressed in the same biological dose units and may therefore be directly compared, one with another.

Isoeffective low- and high-LET treatments must therefore comply by definition with the condition,

$$BED_L = BED_H \quad (11)$$

Equations 7 and 10 as applied to fractionation schedules corresponding to isoeffective low- and high-LET treatments can be respectively rewritten as,

$$\begin{aligned}
 BED_L &= n_L d_L \left(1 + \frac{d_L}{(\alpha/\beta)_L}\right) \Rightarrow \\
 \frac{1}{D_L} &= \frac{1}{BED} + \frac{1}{(\alpha/\beta)_L BED} d_L \quad (12)
 \end{aligned}$$

$$\begin{aligned}
 BED_H &= n_H d_H \left(RBE_{max} + \frac{RBE_{min}^2 d_H}{(\alpha/\beta)_L}\right) \Rightarrow \\
 \frac{1}{D_H} &= \frac{RBE_{max}}{BED} + \frac{RBE_{min}^2}{(\alpha/\beta)_L BED} d_H \quad (13)
 \end{aligned}$$

where the notation has been simplified to  $BED = BED_L = BED_H$ .

Equation 12 is the formulation proposed by Fowler (1989) for use in deriving the  $(\alpha/\beta)$  ratios of tissues treated with isoeffective low-LET fractionated regimes, via the so-called fraction-size effect or 'Fe-plots', which are plots of  $Y =$  reciprocal

total dose against  $X =$  dose-per-fraction. Reciprocal total dose is the same as reciprocal BED only when dose-per-fraction tends to zero, as defined by Barendsen (1982a) for Extrapolated Total Dose (ETD) before it was renamed BED by Fowler (1989). From the intersection of the low-LET Fe-plot on the vertical axis we obtain the reciprocal of the BED associated with the given end point. Knowing the slope of the line, the BED is then used to derive the  $(\alpha/\beta)$  ratio of the tissue. Using Equation 13 the corresponding Fe-plot is derived from the high-LET doses required to achieve the same biological end point. The intersection value and the slope, used in conjunction with the values for BED and  $(\alpha/\beta)$  derived from the low-LET data, allow  $RBE_{max}$  and  $RBE_{min}$  to be derived. Comparing Equations 12 and 13 it is clear that the high-LET slope differs from that for low-LET by a factor of  $RBE_{min}^2$ . Thus, Fe-plots showing little or no change in slope indicate that  $RBE_{min} \sim 1$ , whereas high-LET slopes which are greater or less than the low-LET slopes respectively indicate  $RBE_{min} > 1$  or  $< 1$ .

### Testing of the model against measured data

#### *Mice LD<sub>50</sub> after oesophagus injury*

To illustrate the operation of the above method to calculate  $RBE_{max}$  and  $RBE_{min}$ , it will first be used to derive the RBE for the mouse oesophageal endpoint of LD<sub>50</sub> in 10–40 days (animals which survive this period may die later from radiation pneumonitis) after irradiation of the thorax with 250 kVp X-rays and d(16)Be neutrons. Endpoint doses are available for single doses, two fractions in 24 h, five fractions in 4 days and 10 fractions in 11 days (Hornsey & Field 1979). Figure 1 shows the resultant Fe-plots.

From the X-ray slope and intersection point the derived BED and  $(\alpha/\beta)$  are:

$$\begin{aligned}
 BED &= \frac{1}{0.0112} = 89.54 \text{ Gy} \Rightarrow \\
 (\alpha/\beta)_L &= \frac{1}{BED \cdot 0.007} = \frac{0.0112}{0.007} = 16.25 \text{ Gy}
 \end{aligned}$$

Therefore, from the Fe-plot corresponding to the fast neutrons, the subsequently derived  $RBE_{max}$  and  $RBE_{min}$  are:

$$\begin{aligned}
 RBE_{max} &= 89.54 \times 0.0341 = 3.05 \Rightarrow \\
 RBE_{min} &= \sqrt{BED \times (\alpha/\beta)_L \times 0.0036} = 2.28
 \end{aligned}$$

Substituting the values obtained for  $(\alpha/\beta)_L$ ,  $RBE_{max}$  and  $RBE_{min}$  into Equation 5, the resultant

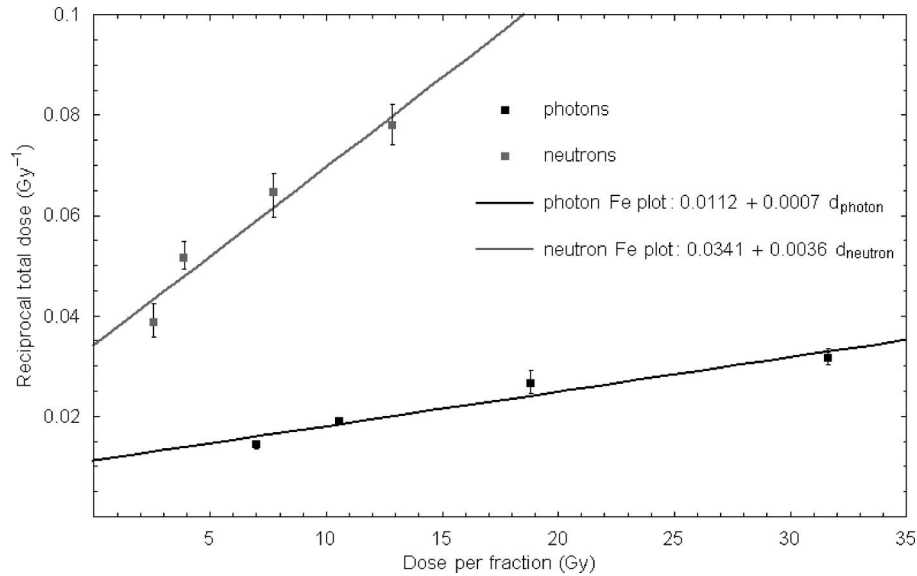


Figure 1. Fe-plots for LD<sub>50</sub> due to oesophagus injury in TO mice after irradiations with X-rays and fast neutrons. Data from Hornsey and Field (1979).

expression for RBE as a function of the X-ray dose per fraction is:

$$RBE = \frac{49.58 + \sqrt{2458.69 + 336.48d_L + 20.71d_L^2}}{32.49 + 2d_L} \quad (14)$$

The resultant RBE curve from Equation 14, along with the original data points, is shown in Figure 2.

The black trace corresponds to the RBE obtained when using  $RBE_{\max}$  and  $RBE_{\min}$  in Equation 5, while the grey line corresponds to the RBE obtained without using the concept of  $RBE_{\min}$  [i.e., that obtained via Equation 6). The RBE difference ( $\Delta RBE$ ) obtained between the two lines at 2 Gy per fraction is 5.2%. This difference is due to the large value of  $RBE_{\min}$  and which reflects the values of RBE at very large doses per fraction reported by Hornsey and Field (1979). The black squares in Figure 2 are the original data points and it is clear that the curve incorporating the  $RBE_{\min}$  concept provides an altogether better fit to the data.

#### Renal damage in mice after fast neutron irradiation

Stewart et al. (1984) reported RBE values for the renal damage of mice irradiated with 3 MeV neutrons based on early and late endpoints of reduction of haematocrit in the kidney to a 40% level (22 weeks) and ethylenediaminetetraacetic acid (EDTA) clearance of 3% retention (28 weeks), respectively. The resultant parameters from the Fe-plot analysis are summarized in Table I and the RBE curves obtained from Equation 5 for each endpoint are shown in Figure 3.

Very little difference was found between considering and not considering  $RBE_{\min}$  in the RBE equation (see Table I), primarily because the fitted  $RBE_{\min}$  value is  $\sim 1$ . Figure 3 suggests that, up to around 25 Gy of X-ray dose, the RBE for early renal damage effects is higher than for late effects.

The data assessed in Figure 3 employed X-ray doses per fraction in the range 4.7–14.4 Gy. In a separate study, Joiner and Johns (1987) investigated the same range of fractional dose sizes for mouse renal damage, but used 1, 2, 5 and 10 fractions and also included 10 fractions plus a “top-up” dose of neutrons in order to measure RBE in the lower X-ray dose range of 0.75–3.0 Gy per fraction. This “top-up” data however has not been included in the present analysis in order to maintain the correspondence with the previous experiments and also to avoid including any low-dose hypersensitivity effects which might be produced by X-rays at very low doses per fraction. Also, RBE has been calculated at different levels of functional effect in order to reproduce the method used by Joiner and Johns. The resultant  $RBE_{\max}$  and  $RBE_{\min}$  calculated for these levels are shown in Table I. The value of  $RBE_{\max}$  and  $(\alpha/\beta)$  calculated here are 15.85 and 2.23 Gy respectively, these values being in accordance with the values proposed by Joiner and Johns (see bracketed values in Table I). The fitted RBE versus dose-per-fraction curves are shown in Figure 4.

#### Colo-rectal injury in mice

Terry et al. (1983a, 1983b) studied the RBE of early- and late-effects in colo-rectal normal tissue after

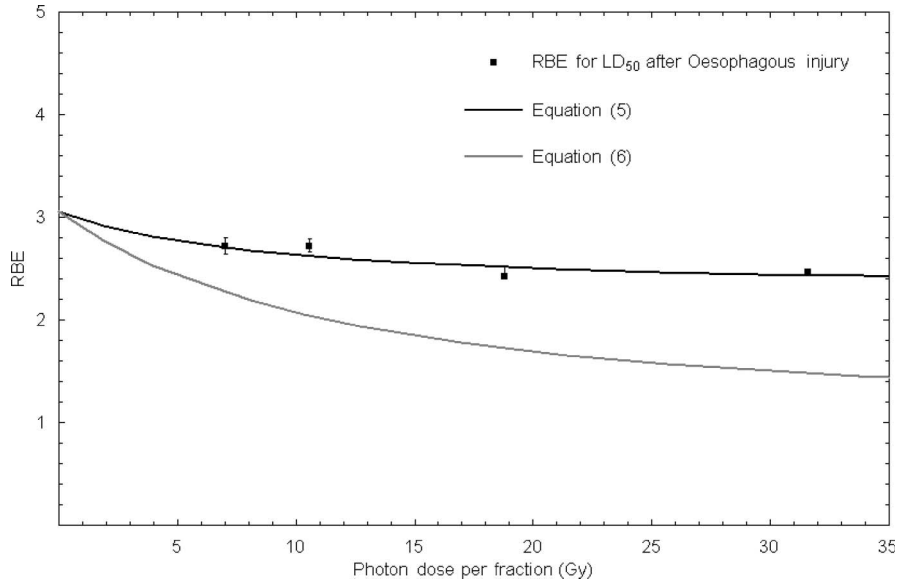


Figure 2. Data points show the RBE variation with dose derived from the data plotted in Figure 1. The black line is derived from Equation 5 and incorporates a fitted value of  $RBE_{min}$  whilst the grey line assumes that  $RBE_{min}$  is unity. The better match of the measured data to the former is apparent.

Table I. Relevant radiobiological parameters obtained from Equations 12 and 13 for the different end-points selected. The values in round brackets correspond to the published values. In the final two columns are listed the two-tailed  $t$  and (in square brackets) the associated  $p$  values of the fit of the data points to the two alternative models [Weatherbum (1962)]. For all of the data analysed the complex model (i.e., that including both  $RBE_{max}$  and  $RBE_{min}$ ) provides the better statistical fit, although only in the case of oesophagus LD50 data is the fit very highly significant.

End point	$(\alpha/\beta)_L$ [Gy]	$BED_L$ (d→0 Gy) [Gy]	$RBE_{max}$	$RBE_{min}$	$t$ [ $p_{two-tailed}$ ] ( $RBE_{min}$ , $RBE_{max}$ )	$t$ [ $p_{two-tailed}$ ] ( $RBE_{max}$ )
LD <sub>50</sub> – Oesophagus injury (Hornsey & Field 1979)	16.24	89.54	3.05	2.27	0.1348 [0.9013]	6.4745 [0.0075]
40% Residual Haematocrit (Stewart et al. 1984)	1.15	178.65	26.33	1.19	0.1678 [0.8774]	0.3223 [0.7684]
3% Residual EDTA (Stewart et al. 1984)	1.22	183.74	20.58	1.35	0.6348 [0.5706]	6.2033 [0.0084]
Mouse kidney (Joiner & Johns 1987)	2.23 (3.04 ± 0.35)	115.48	15.85 (11.65 ± 0.69)	0.73	0.4029 [0.6898]	0.9594 [0.3450]
Mouse skin injury (Joiner et al. 1983)	17.42 (43.6)	60.69	5.35 (7.2)	0.41	1.1813 [0.2486]	1.9109 [0.0675]
Colo-rectal injury (Nadir body weight) (Terry et al. 1983b)	12.33 (13.07)	70.50 (67.11)	7.04 (8.5)	0.47	0.7401 [0.4688]	3.4067 [0.0031]
Colo-rectal injury (Peak body weight) (Terry et al. 1983b)	7.38 (9.21)	82.10 (85.47)	6.84 (5.7)	0	1.0803 [0.3012]	2.2668 [0.0427]
LD <sub>50</sub> – Colo-rectal injury (2 months) (Terry et al. 1983)	28.69 (28.63)	76.68 (76.92)	5.7 (5.7)	1.46	0.0925 [0.9321]	0.5223 [0.6376]
LD <sub>50</sub> – Colo-rectal injury (15 months) (Terry et al. 1983)	3.11 (3.12)	108.24 (107.87)	12.56 (12.70)	0.41	0.2503 [0.8185]	1.2076 [0.3137]
BR × 1.1 – Lung injury (28 weeks) (Parkins et al. 1985)	2.93 (2.9)	50.04	7.63	0.58	0.5920 [0.5755]	1.0587 [0.3304]
BR × 1.1 – Lung injury (68 weeks) (Parkins et al. 1985)	2.14 (2.1)	54.11	9.22	0.10	0.8678 [0.4188]	2.9749 [0.0248]
LD <sub>50</sub> – Lung injury (28 weeks) (Parkins et al. 1985)	5.95 (4.5)	38.51	5.19	0.99	0.7143 [0.5018]	0.6987 [0.5190]
LD <sub>50</sub> – Lung injury (68 weeks) (Parkins et al. 1985)	2.32 (2.15)	56.18	8.62	0.72	0.5789 [0.5837]	1.9497 [0.0991]
Desquamation – Pig skin injury (Hopewell et al. 1988)	15.17	79.05	3.46 (2.75)	0.71	0.0227 [0.9827]	0.5692 [0.5938]
Necrosis – Pig skin injury (Hopewell et al. 1988)	5.25	101.27	4.26 (4.32 ± 0.39)	0.91	0.3146 [0.7657]	0.4138 [0.6962]

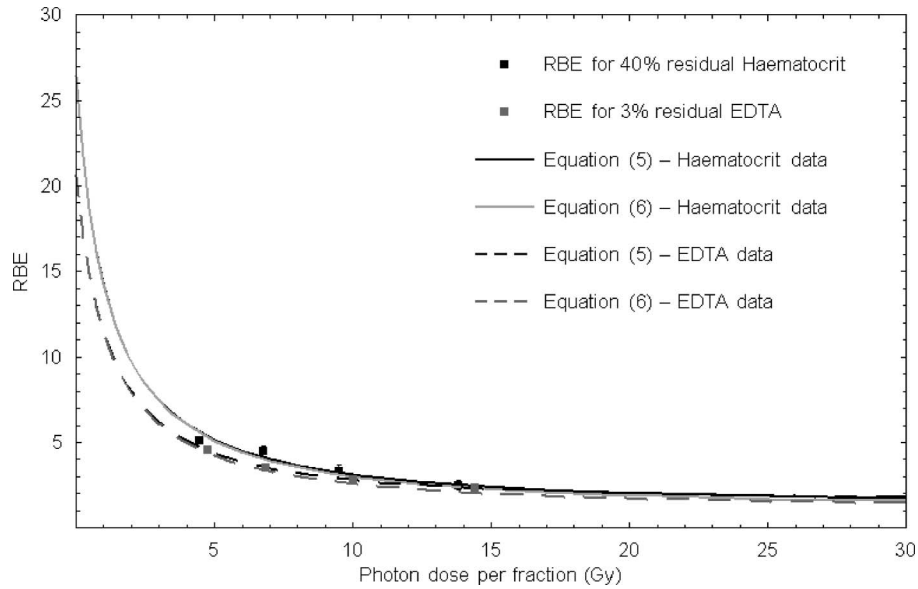


Figure 3. RBE versus dose curves for Haematocrit reduction to 40% level (early reaction – 22 weeks) and 3% ethylenediaminetetraacetic acid retention (late reaction – 28 weeks) for mice kidney after being irradiated with X-rays and fast neutrons. The fitted curves (respectively black and grey) are derived from Equation 5. Data from Stewart et al. (1984).

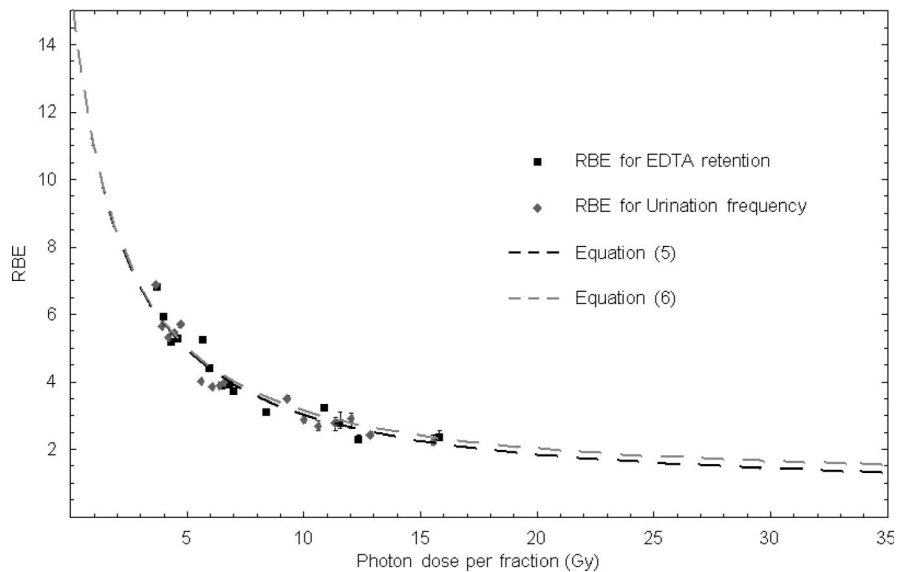


Figure 4. RBE versus dose curves corresponding to mouse kidney damage for X-rays and fast neutrons. The black squares are the data points obtained from the ethylenediaminetetraacetic acid clearance experiments, while the grey diamonds represent the data extracted from the urination frequency experiments. The black line corresponds to the RBE-fitted curve which includes  $RBE_{\min}$ , whilst the grey line corresponds to the calculation without taking  $RBE_{\min}$  into account. Data from Joiner and Johns (1987).

irradiation of mice with  $^{137}\text{Cs}$  gamma-rays and fast neutrons. The end points used were:

- **Body weight:** The weight lost shortly after irradiation and the maximum body weight regained were both studied as a function of radiation dose. The nadir in weight occurred between 11 and 17 days (early effect), and the maximum body weight was achieved at 4–7 months after irradiation (late effect).
- **Lethality:** The proportion of surviving animals was assessed sequentially at monthly intervals up to 16 months after irradiation. The lethal total dose required to kill 50% of the mice population ( $LD_{50}$ ) values were obtained at 15 days and 15 months after irradiation with both  $\gamma$ -rays and neutrons.

Table I summarizes the results obtained from the present analysis and the results determined by Terry et al. The associated RBE curves to the relevant end

point (with and without the  $RBE_{min}$  concept) are presented in Figures 5 and 6.

In both Figures major differences are only noted at doses-per-fraction larger than 10 Gy. A notable feature in Figure 6 however, is the existence of a certain threshold dose/fraction ( $\approx 5$  Gy) above which the late-reacting RBE is lower than that for the acute response. As the fractionation response of most tumours is similar to that of acute-responding normal tissues then this divergence in RBE values might have important implications for therapy. To avoid more damage to the normal tissue than tumour, the doses/fraction required would have to be  $> 5$  Gy, as lower doses would infer a higher RBE for normal tissues and higher toxicity. It is also interesting to notice how the difference between the early and late effects tend to increase for any given dose per fraction when  $RBE_{min}$  is included in Equation 5.

#### Damage to mouse lung

Parkins et al. (1985) measured lung damage after exposing the thorax of CBA/Ht male mice to 240 kVp X-rays and 3 MeV neutrons. The end points used were increase of breathing rate (by a factor 1.1 with respect the normal rate) and lethality ( $LD_{50}$ ). The RBE curves for these are respectively presented in Figures 7 and 8.

In Figure 7, the RBE curves associated with increased breathing rates at early and late stages of the experiment shows a distinction between the cases

corresponding to inclusion or non-inclusion of  $RBE_{min}$  in Equation 5. The largest difference is observed in the late effects, but this difference is significant only at high doses per fractions. The implication is that treatment with neutrons would be beneficial only if the doses per fraction were larger than  $\sim 3$  Gy. It is clear from the  $p$  values in Table I that a better fit to the RBE points is achieved when considering  $RBE_{min}$  in Equation 5. That can be seen from the points at higher doses per fractions and which lay well under the early- and late-RBE curves which do not include  $RBE_{min}$ .

In Figure 8 the same difference between considering and not considering  $RBE_{min}$  is observed in the case of late end points but it is not as great in the case of early end points, for which the associated RBE curves are almost perfectly coincident. Adverse therapeutic index is likely at fractional dose less than about 4 Gy.

#### Acute skin reactions in:

- *Pig skin.* Hopewell et al. (1988) exposed pig skin to different fractionated doses of 250 kV X-rays and  $d(42)Be$  neutrons in order to investigate the respective early and late end-point RBE of pig skin desquamation and necrosis. The data from that study are presented in Figure 9, together with the RBE curves derived using the present analysis. Small differences between inclusion and non-inclusion of  $RBE_{min}$  are apparent at higher fractional doses. A positive therapeutic

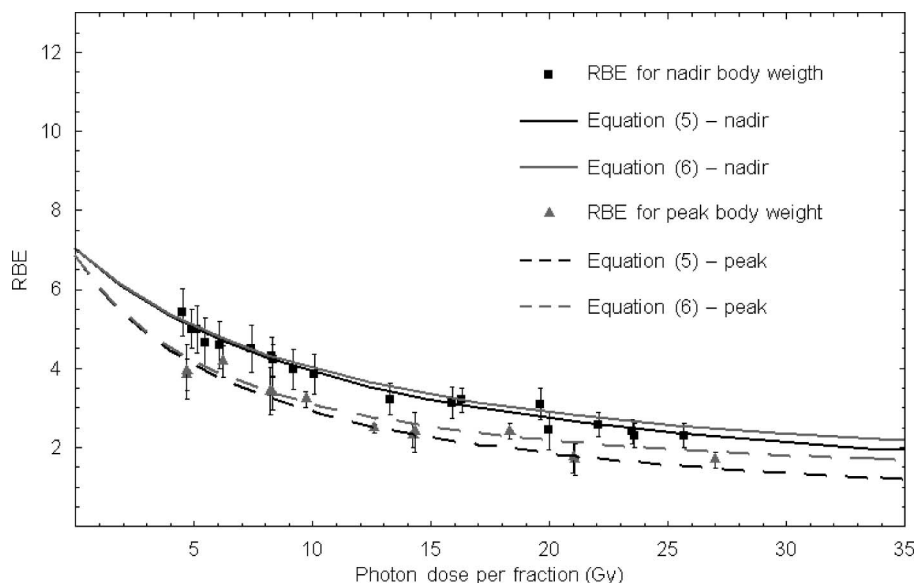


Figure 5. RBE versus dose curves for changes in body weight as a consequence of colo-rectal damage after pelvic irradiation. The black squares represent the data points for the lower limit of body weight attained, while the grey triangles are for the higher limit. The biggest differences between the predicted curves obtained from Equation 5 and 6 are noticeable at doses per fraction  $> 10$  Gy. According to this figure, the use of neutron is contraindicated as the RBE for early effects is higher than for late effects at any given dose per fraction. Data from Terry et al. (1983a, 1983b).

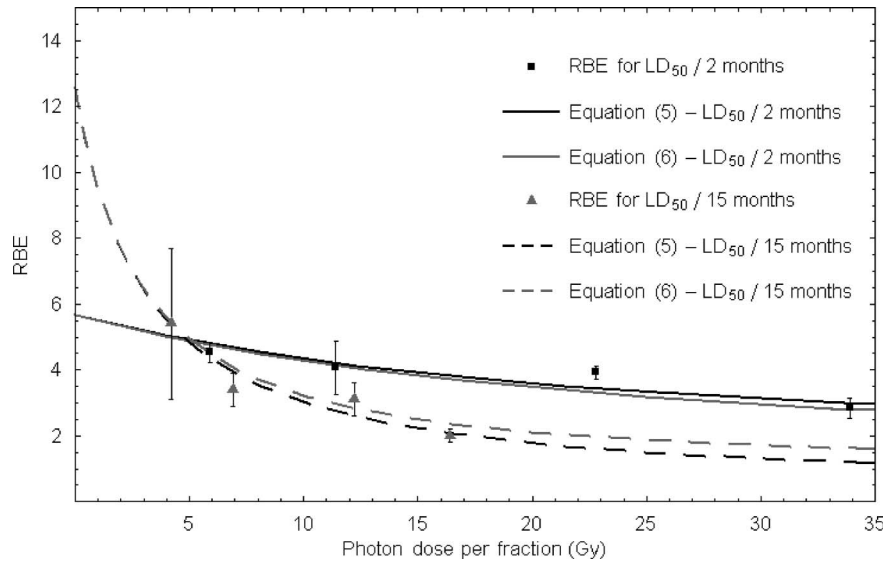


Figure 6. RBE versus dose for LD<sub>50</sub> following colo-rectal damage. Squares correspond to data for early effects while triangles correspond to late effects. The solid lines are fitted to the former data and the dotted lines to the latter. The data implies that favourable disposition of the RBE effect (assuming that tumours would behave similarly to the acute effects) is achievable only above 5 Gy. Data from Terry et al. (1983a, 1983b).

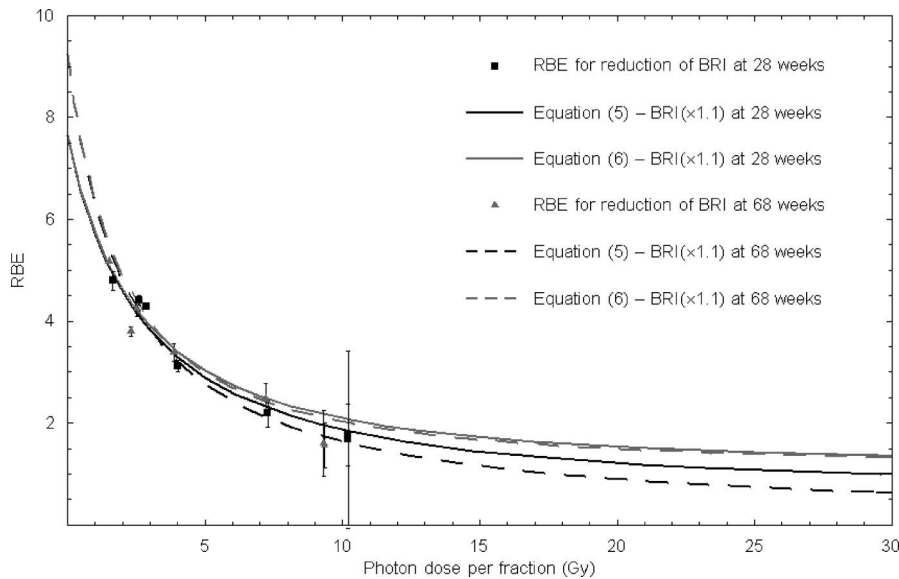


Figure 7. RBE versus dose for increased breath rate by a factor of 1.1 following exposure of whole mouse thorax to X-rays and neutrons. Squares correspond to early (28 weeks) data endpoint while triangles correspond to late (68 weeks) endpoint. Data from Parkins et al. (1985).

ratio will only be valid for doses greater than  $\sim 2$  Gy.

- *Mouse skin.* Other useful data on normal tissue effects was produced by Joiner et al. (1983) using neutrons from the 4 MV van de Graaf accelerator at the Gray Laboratory. Two different experiments were performed, one where single, two or five equal fractions were delivered daily, and a repeat experiment that included 9 equal fractions, the dose being delivered twice per day with an inter-fraction interval of at least

6 h. The data analysis and curve fitting was performed slightly differently in this case in order to reproduce the method used by Joiner. The RBE were calculated for different skin reaction levels from 0.8–2.4, the resultant  $RBE_{max}$  and  $RBE_{min}$  values being as listed in Table I and the RBE curve fits being shown in Figure 10.

For comparison purposes, we have included the RBE curves for EDTA retention shown in Figure 4.

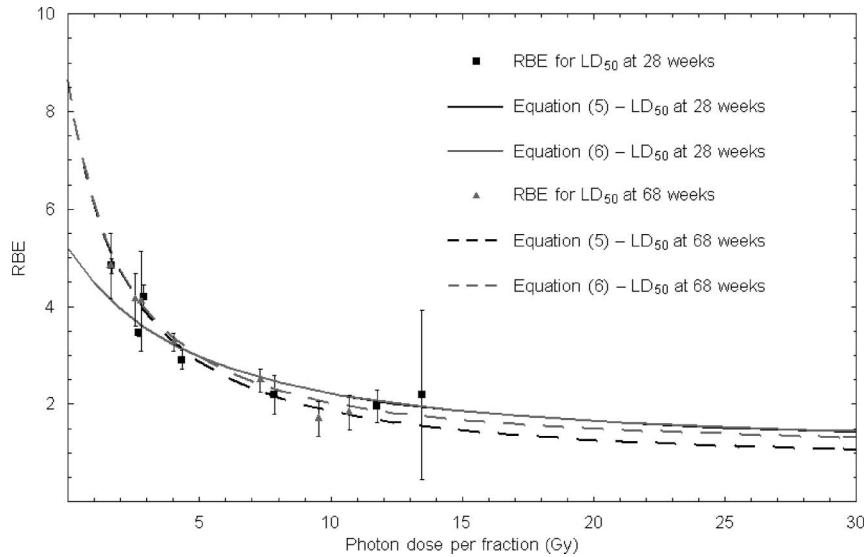


Figure 8. RBE versus dose for LD<sub>50</sub> determinations following exposure to X-rays and neutrons of whole mouse thorax. Squares correspond to early (28 weeks) end point while triangles correspond to late (68 weeks) end point. Data from Parkins et al. (1985).

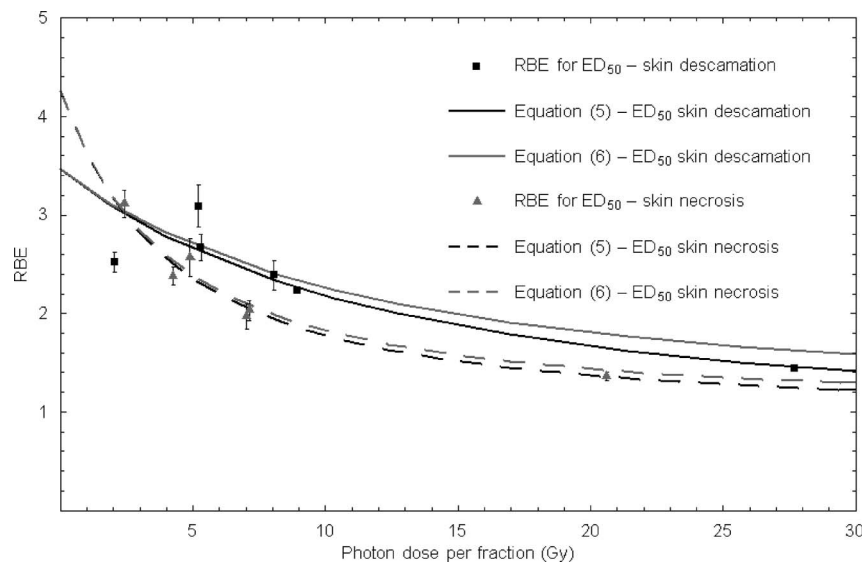


Figure 9. ED<sub>50</sub> after exposure to X-rays and neutrons of pig skin. Squares correspond to early end point (desquamation) while triangles correspond to late end point (necrosis). Data from Hopewell et al. (1988).

This shows that in these circumstances, a positive therapeutic ratio can only be achieved at doses higher than  $\sim 7$  Gy.

#### Overall results and comparison with predicted values

Figures 6 to 10 show a general agreement of a higher RBE for late effects at the levels of dose per fraction conventionally used in clinical radiotherapy. Although these results are not conclusive, they corroborate earlier suggestions that the reason for adversity when using neutrons is a consequence of the greater impact they have on normal tissues

at lower fractional doses. The Hammersmith neutron trials in the 1970s (Catterall & Bewley 1979) are often considered to be disappointing because, although the tumour control in advanced head and neck cancer increased by a factor of four (from 12/62 to 54/71; Catterall 1989), so did the late complications (from 4–17%), the latter figure being considered unacceptably high and adding to the general impression that neutron therapy failed to match expectations. The Edinburgh neutron trials used lower fractional doses but failed to indicate an improved therapeutic ratio (Duncan 1994).

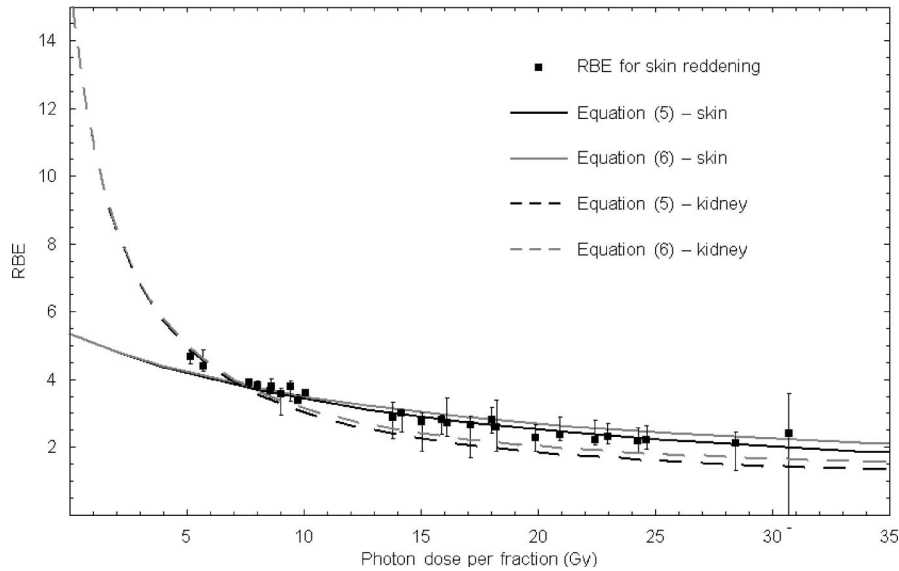


Figure 10. RBE versus dose corresponding to mice skin exposed to X-rays and fast neutrons. The back boxes represent the data obtained from the experiment using one, two or five daily fractions; the grey triangles represent the data extracted from the second experiment which included up to 9 fractions. The black solid line corresponds to the RBE fitted curve which includes  $RBE_{\min}$ , while the grey solid line corresponds to the calculation without taking  $RBE_{\min}$  into account. Data from Joiner et al. (1983).

Table I summarizes the results obtained from the present analysis and compares them with the measured data points. In the final two columns are listed the two-tailed  $t$  and (in square brackets) the associated  $p$  values of the fit of the data points to the two alternative models. For all of the data analysed the complex model (i.e., that including both  $RBE_{\max}$  and  $RBE_{\min}$ ) provides the better statistical fit, although only in the case of oesophagus LD50 data is the fit very highly significant.

For this particular tissue, the difference in RBE at a dose per fraction of 2 Gy of X-rays between the two traces shown in Figure 2 is 5.15%. In the rest of the tissues analysed  $\Delta RBE|_{2\text{Gy}}$  is minimal. However, it is interesting to notice how the presence of  $RBE_{\min}$  in Equation 5 makes a bigger change to the RBE of late effects than to those of the early effects. In all the cases analysed, the RBE late effect changes are smaller when  $RBE_{\min}$  is taken into account. This means that, if the RBE curves for early and late effects cross over at some point, the dose-per-fraction at which they cross could be shifted towards lower doses, which ultimately would affect the lower limiting dose required to achieve a positive therapeutic ratio. Conversely, had the RBE changes for late effects been larger when considering  $RBE_{\min}$  in Equation 5, the crossing point between early and late reaction curves would have shifted to higher doses-per-fraction. It is still not clear why, or in what cases, the  $RBE_{\min}$  correction increases the change in RBE in some cases and decreases it in others. The present authors are investigating this

effect using data produced with other tissues and radiation qualities.

## Discussion

A method is proposed for calculating RBE values using the assumption that the main radiosensitivity parameters describing the LQ model,  $\alpha$  and  $\beta$ , are both susceptible to change with changing LET. As indicated in a previous paper (Dale & Jones 1999), several authors have shown experimentally that the  $\beta$ -values for some cell lines appear to be LET-dependent (Kellerer & Rossi 1972, Goodhead 1988, Stenerlöv et al. 1995). As discussed here, a consequence of that is the requirement to consider two intrinsic RBE values ( $RBE_{\max}$  and  $RBE_{\min}$ ) for every cell line and which, as demonstrated in Figure 2, could have an important impact in calculating the relative effectiveness of a given high-LET dose. In order to obtain a high TCP while keeping an NTCP as low as possible, it is essential in radiotherapy to keep the normal tissue dose well below its tolerance limit. This principle is valid whatever the radiation type is used and Figures 6–10 suggest that neutrons may produce more damage in normal tissue than in tumour for the doses per fraction normally used in radiotherapy. This might be an indication of the reasons why the UK neutron trial experience was disappointing although, perhaps, any radiobiological shortcomings may well have been exacerbated by a poorly-penetrating and heterogeneous neutron beam.

Several points arise from this analysis. Most of the cases reviewed do not show a tremendous difference between the plots produced with and without the  $RBE_{min}$  included in Equation 5 and, even then, the difference is noticed only at high fractional doses. However, the fact that, in the oesophagus case in particular, there is a significant difference suggests that the  $RBE_{min}$  might well be a parameter that must be more generally taken into account to avoid the risk of underestimating RBE at low fractional doses, particularly in critical organs. It follows then that the general consensus of considering  $\beta$  independent of LET might be inappropriate for some high-LET radiotherapy. One advantage of our revised model is that it does not require any additional clinical data from isoeffect or other studies and it therefore can serve to increase the clinical utility of BED/RBE iso-effect formulations, the potential usefulness of which were first identified by Barendsen (1982a). The overall variation of  $\beta$  with LET is in any case likely to be small and this *may* explain why derived  $RBE_{min}$  values, as seen from Table I, are both greater and less than unity (the majority being in the latter category). In addition to the possibility of a systematic dependence of  $\beta$  on LET there are a number of other influences which may affect the magnitude of the observed variations, e.g., measurement imprecision, variable radiosensitivity, breakdown of the LQ model at high doses, etc., and the

finding of  $\beta$ -values either side of unity does mean that experimental imprecision and/or modelling limitations cannot be ruled out.

There is also the issue of the statistical significance of the raw data. Although Fe-plots have been used for many years to estimate the  $(\alpha/\beta)$  parameter (e.g., Douglas & Fowler 1976), several authors have commented on the statistical shortcomings of this method (Tucker 1984, de Boer 1988, Taylor & Kim 1989). Some of these criticisms are: (i) The method derives the  $(\alpha/\beta)$  parameter via a two-stage (indirect) analysis, (Fischer & Fischer 1977, Herring 1980); and (ii) the method tends to be biased in its estimation of  $(\alpha/\beta)$  as a consequence of the uncertainty in both, the independent and the dependent variables ( $d$  and  $1/TD$  respectively). This double uncertainty precludes the use of linear regression analysis [which may be applied only if the experimental uncertainty is restricted to the values of the ordinate (de Boer 1988)] and forces the use of non-linear analysis (Tucker 1984). However, Fe-plots do use clinically relevant data (dose per fraction and iso-effective total doses) and link it with BED, a parameter of widely recognized value and which is very helpful when comparing isoeffective treatments. de Boer (1988) proposed a method based again on a linear least-square fit of data presented as a TD vs.  $d \cdot TD$  plot, which provided values of  $E/\alpha$  and  $(\alpha/\beta)$  very similar to those derived from non-linear

Table II. Relevant radiobiological parameters obtained when applying de Boer's method.

End point	$(\alpha/\beta)_L$ [Gy]	$BED_L$ ( $d \rightarrow 0$ Gy) [Gy]	$RBE_{max}$	$RBE_{min}$	$t [p]$ ( $RBE_{min}, RBE_{max}$ )	$t [p]$ ( $RBE_{max}$ )
LD <sub>50</sub> – Oesophagus injury (Hornsey & Field 1979)	14.87	94.38	3.10	2.28	0.0576 [0.9579]	6.5641 [0.0072]
40% Residual Haematocrit (Stewart et al. 1984)	1.47	145.07	21.23	1.02	0.6676 [0.5521]	0.7155 [0.5960]
3% Residual EDTA (Stewart et al. 1984)	1.17	190.84	21.30	1.25	3.4072 [0.0422]	5.7134 [0.0106]
Mouse skin injury (Joiner et al. 1983)	46.21	45.27	4.12	0.17	24.29 [0.8098]	0.0264 [0.9790]
Mouse kidney (Joiner & Johns 1987)	29.18	36.27	5.06	0.15	0.2429 [0.8098]	0.0264 [0.9791]
LD <sub>50</sub> – Colo-rectal injury (2 months) (Terry et al. 1983)	34.39	72.04	5.35	1.52	0.0583 [0.9571]	0.8018 [0.4813]
LD <sub>50</sub> – Colo-rectal injury (15 months) (Terry et al. 1983)	5.49	73.95	8.54	0.17	0.4031 [0.7139]	0.4677 [0.6719]
BR × 1.1 – Lung injury (28 weeks) (Parkins et al. 1985)	3.19	47.82	7.29	0.32	0.7726 [0.4691]	0.9916 [0.3697]
BR × 1.1 – Lung injury (68 weeks) (Parkins et al. 1985)	3.61	39.55	6.74	0.07	0.1283 [0.9021]	0.1771 [0.2837]
LD <sub>50</sub> – Lung injury (28 weeks) (Parkins et al. 1985)	5.81	39.33	5.31	0.40	1.5105 [0.1817]	0.4634 [0.6594]
LD <sub>50</sub> – Lung injury (68 weeks) (Parkins et al. 1985)	3.11	47.12	7.22	0.43	2.1008 [0.0804]	0.7342 [0.4905]
Desquamation – Pig skin injury (Hopewell et al. 1988)	17.72	75.54	3.29	0.17	0.7262 [0.5002]	0.3454 [0.7438]
Necrosis – Pig skin injury (Hopewell et al. 1988)	5.42	100.1	4.21	0.39	3.2473 [0.0228]	0.4723 [0.6566]

statistical methods. Table II shows the result of using the de Boer method to reassess the Fe-derived parameters listed in Table I. No significant variations are observed, suggesting that the use of Fe-plots is justified in this analysis.

A final comment needs to be made on the use of Equation 5 to obtain isoeffective fractionation schemes between high- and low-LET radiotherapy. The equation provides a first estimate of the RBE as a function of low-LET parameters, thus making it simpler to use clinically, but a number of adjustments might in future need to be made to this equation. Ideally, Equation 5 should be extended to consider the different RBE effects produced by the  $\gamma$ -contamination typically existing in a neutron beam since the equation is presently not designed for mixed-LET beams. It is highly likely that the neutron beams used in the experiments considered in this article possessed low-LET photon contamination. However, the applications discussed here, and the consequent clinical implications, do not require such resolution since, at this preliminary level, empirical correlations to “whole beams” are being assessed.

For those treatments where a mixture of radiation types is required it will be necessary to consider the dependency of RBE with LET. In a previous paper (Dale & Jones 1999), the Microdosimetric-Kinetic (MK) model (Hawkins 2003) was suggested as providing a good explanation of this dependency. However, the MK model itself leads to the implication that  $\beta$  is independent of LET. Thus, from what has been suggested in this paper, the philosophy embodied within the MK model itself may need to be reconsidered. In clinical practice, Equation 5 can be used as the first approach to finding the ‘clinical RBE’ (Barendsen [1982b], Wambersie [1999]) and then later readjusted as the result of clinical experience (e.g., dose escalation phase I studies) built up from treatments using that particular high-LET.

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### References

Barendsen GW. 1982a. Dose fractionation, dose-rate and iso-effect relationships for normal tissue responses. *International Journal of Radiation Oncology Biology Physics* 8:1981–1997.

Barendsen GW. 1982b. Radiobiology of neutrons. *International Journal of Radiation Oncology Biology Physics* 8:2103–2107.

de Boer RW. 1988. The use of the  $D$  versus  $dD$  plot to estimate the  $\alpha/\beta$  ratio from isoeffect radiation damage data. *Radiation Oncology* 11:361–367.

Catterall M, Bewley DK. 1979. *Fast neutrons in the treatment of Cancer*. London: Academic Press.

Catterall M. 1989. Neutron therapy at Hammersmith Hospital 1970 to 1985. A re-examination of results. *Strahlentherapie und Onkologie* 165:298–301.

Dale RG, Jones B. 1999. The assessment of RBE effects using the concept of Biologically Effective Dose. *International Journal Radiation Oncology Biology Physics* 43(3):639–645.

Douglas BG, Fowler JF. 1976. The effect of multiple small doses of X rays on skin reactions in the mouse and a basic interpretation. *Radiation Research* 66:401–426.

Duncan W. 1994. An evaluation of the results of neutron therapy. *Acta Oncologica* 33:299–306.

Fischer DB, Fischer JJ. 1977. Dose response relationships in radiotherapy: Applications of a logistic regression model. *International Journal of Radiation Oncology Biology Physics* 2(7–8):773–781.

Fowler JF. 1989. The linear-quadratic formula and progress in fractionated radiotherapy. *British Journal of Radiology* 62: 679–694.

Goodhead DT. 1977. Inactivation and mutation of cultured mammalian cells by aluminium characteristic ultrasoft X-rays: III. Implications of the theory of dual radiation action. *International Journal of Radiation Biology* 32(1):43–70.

Goodhead DT. 1988. Inactivation and mutation of cultured mammalian cells by aluminium characteristic ultrasoft X-rays. III. Implications for theory of dual radiation action. *International Journal of Radiation Biology* 32(1):43–70.

Hawkins RB. 2003. A microdosimetric-kinetic model for the effect of non-Poisson distribution of lethal lesions on the variation of RBE with LET. *Radiation Research* 160:61–69.

Herring DF. 1980. Methods for extracting dose response curves from radiation therapy data. I. A unified method. *International Journal Radiation Oncology Biology Physics* 6(2):225–232.

Hornsey S, Field SB. 1979. The effects of single and fractionated doses of X-Rays and neutrons on the oesophagus. *European Journal of Cancer* 15:491–498.

Hopewell KW, Barnes DWH, Robbins MEC, Sansom JM, Knowles JF, van den Aardweg GJM. 1988. The relative biological effectiveness of fractionated doses of fast neutrons (42 MeV<sub>d→Be</sub>) for normal tissues in the pig. I. Effects on the epidermis and dermal vascular/connective tissues. *British Journal of Radiology* 61:928–938.

Joiner MC, Mauhgan RL, Fowler JF, Denekamp J. 1983. The RBE for Mouse Skin irradiated with 3-MeV neutrons: Single and fractionated doses. *Radiation Research* 95:130–141.

Joiner MC, Johns H. 1987. Renal damage in the mouse: The effect of d(4)-Be neutrons. *Radiation Research* 109:456–468.

Joiner MC, Bentzen SM. 2002. Time-dose relationships: The linear-quadratic approach. In: GG Steel, editor. *Basic clinical radiobiology*. 3rd ed. London: Edward Arnold. pp 120–133.

Kellerer AM, Rossi HH. 1972. The theory of dual radiation action. *Current Topics in Radiation Research Quarterly* 8:85–158.

Parkins CS, Fowler JF, Maughan RL, Roper MJ. 1985. Repair in mouse lung for up to 20 fractions of X rays or neutrons. *British Journal of Radiology* 58:225–241.

Stenerlöw B, Petterson O-A, Essand M, Blomquist E, Carlson J. 1995. Irregular variations in radiation sensitivity when the linear energy transfer is increased. *Radiotherapy and Oncology* 36:133–142.

Stewart FA, Soranson J, Maughan R, Alpen EL, Denekamp J. 1984. The RBE for renal damage after irradiation with 3 MeV neutrons. *British Journal of Radiology* 57:1009–1021.

Taylor JMG, Kim DK. 1989. The poor statistical properties of the Fe-plot. *International Journal Radiation Biology* 56(2): 161–167.

Terry NHA, Denekamp J, Maughan RL. 1983a. RBE values for colo-rectal injury after caesium 137 gamma-ray and neutron irradiation. I. Single doses. *British Journal of Radiology* 56: 257–265.

- Terry NHA, Denekamp J, Maughan RL. 1983b. RBE values for colo-rectal injury after caesium 137 gamma-ray and neutron irradiation. II. Fractionation up to ten doses. *British Journal of Radiology* 57:617–629.
- Tucker SL. 1984. Tests for the fit of the Linear-Quadratic model to radiation isoeffect data. *International Journal of Radiation Oncology Biology Physics* 10(10):1933–1939.
- Wambersie A. 1999. RBE, reference RBE and clinical RBE: Applications of these concepts in Hadron therapy. *Strahlentherapie und Onkologie* 175(Suppl. II):39–43.
- Weatherburn CE. 1962. *A first course in mathematical statistics*. 2nd ed, reprinted. Cambridge, UK: Cambridge University Press.