Letter to the Editor

Estimating RBEs at clinical doses from microdosimetric spectra

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To the Editor,

Microdosimetry is perhaps the most useful tool for intercomparing the different types of radiation that are used in radiotherapy; the relative effects of different radiations are controlled by the different initial energy deposition patterns in cellular targets—the subject matter of microdosimetry.[1] It is therefore appropriate that many authors have measured microdosimetric spectra in clinical beams, and have used these data in an attempt to predict clinically relevant relative biological effectiveness (RBE).[2–20]

It appears, however, that a particular formalism that has been used by a number of authors[2–11] to calculate RBEs at clinical doses based on microdosimetric spectra is, in some important respects, incorrect. Here we discuss this issue, but point out that a correct application of microdosimetric theory does indeed allow predictions of RBE, both at low doses and at clinically relevant doses, based on measured microdosimetric spectra.

Before commenting on the formalism that has appeared in the literature, we briefly review the fundamentals of microdosimetric theory as they apply to the predictions of RBE. The fundamental assumption is that relative biological effects are determined by the different energy deposition patterns that different radiations deposit in cellular targets. These energy deposition patterns are quantified through the stochastic quantity specific energy (z), defined as the energy per unit mass deposited in a particular cellular target.[1] After exposure to a dose D of radiation type i, the probability density function of z in a set of cellular targets is given by the Poisson-weighted sum of the effects of different numbers of independent tracks passing through the targets:

$$f_i(z;D)=\sum_{\nu=0}^{\infty}\left[e^{-n}\frac{n^{\nu}}{\nu!}\right]f_i^{(\nu)}(z), \tag{1}$$

where $f_i^{(\nu)}(z)$ represents the probability that a specific energy z is deposited by exactly ν independent tracks passing through a cellular target, and

$$n=D/z_{1F},$$

where

$$z_{1F}=\int z\, f_i^{(1)}(z)dz \Big/ \int f_i^{(1)}(z)dz. \tag{2}$$

Now, given the assumption that relative biological effects are determined by the energy deposition patterns that different radiations deposit in cellular targets, the biological effect of a dose D of radiation i can be written[20] as

$$E_i(D)=\int \epsilon(z)f_i(z;D)dz, \tag{3}$$

where $\epsilon(z)$ is the response of an individual cellular target to a specific energy deposition z. From Eqs. (1) and (3), for very small doses where multiple traversals of the cellular target are unlikely,[20]

$$E_i(D)\approx D\int \epsilon(z)f_i^{(1)}(z)/z_{1F}\, dz. \tag{4}$$

Thus the response per unit dose at low doses, R_i (often termed the ''initial slope''), to a particular radiation, i, can be written as

$$R_i=\int \epsilon(y)f_i(y)/y_F\, dy, \tag{5}$$

where y is the stochastic quantity lineal energy,[1] defined as the energy deposited by a *single track*, divided by the average path length in the cellular target, and y_F is defined analogously to z_{1F}. For single tracks only, y and z can be used interchangeably as there is a linear relationship between them.[1] $f_i(y)$ is often referred to as a microdosimetric single-event spectrum; it can be measured using a low-pressure proportional counter.[1]

Equation (5) can be rewritten as[21]

$$R_i=\int w(y)d_i(y)dy, \tag{6}$$

where $w(y)=\epsilon(y)/y$, and $d_i(y)=yf_i(y)/y_F$. Similarly, Eq. (3) can be rewritten as[22]

$$E_i(D)=\int zw(z)f_i(z;D)dz. \tag{7}$$

As we will discuss, Eqs. (6) and (7) represent a basis for microdosimetric evaluations of RBE at low and at clinically relevant doses, respectively.

Schmidt and Hess,[2] Pihet *et al.*,[3] as well as many subsequent authors,[4–11] have suggested that RBEs at clinically relevant doses can be estimated using

$$\mathrm{RBE}_i(D_0)=\int r(y;D_0)d_i(y)dy, \tag{8}$$

where $\mathrm{RBE}_i(D_0)$ is the RBE of radiation type i, relative to the effects of a reference radiation at a given dose D_0, and $d_i(y)$ is the corresponding microdosimetric single-event spectrum, as described above; $r(y;D_0)$ in Eq. (8) is described as an empirical biological response function specific

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to the dose D_0 of the reference radiation.[3] For example, Pihet *et al.*[3] derived an $r(y;D_0)$ function based on measured RBEs relative to the effects of 8 Gy of p(65)-Be fast neutrons.

However, while Eq. (8) shows a *prima facie* similarity to Eq. (6), Eq. (8) cannot be applied to situations involving high doses of radiation [such as 8 Gy of p(65)-Be fast neutrons, where an average of about 20 neutrons would traverse a 2-μm-diam target[18]], where the low-dose assumptions needed to derive Eq. (6) are not valid. This is directly apparent by noting that $d_i(y)$ in Eq. (8) refers to the spectrum of *single-event* energy depositions in cellular targets, whereas at clinical doses, these targets will be subject to a (different) spectrum of *multievent* energy depositions.

At low doses Eq. (6) can be used to estimate the quantity R_j/R_k, which is the ratio of the low-dose responses (initial slopes) of the two radiations, and is thus the low-dose RBE ($\mathrm{RBE}_{\max}$) of radiation k relative to radiation j. This quantity is not, however, the RBE at high (clinical) doses.

From a clinical perspective, the low-dose RBE is not directly relevant. However, Eqs. (6) and (7) can be used to estimate high dose RBEs as follows:

(A) For the end point in question, first estimate the $w(z)$ response function by unfolding it from either Eq. (6), based on low-dose biological data on single-event microdosimetric data,[21,23,24] or by unfolding it from Eq. (7) using high-dose data biological data and multievent microdosimetric data;[22] standard computer programs exist for calculating multi event spectra, $f_i(z;D)$ from single-event spectra $d_i(y)$.[25]

(B) For a given reference radiation dose D_j, find the RBE, D_j/D_k, such that [see Eq. (7)],

$$\int zw(z)f_j(z;D_j)dz=\int zw(z)f_k(z;D_k)dz. \tag{9}$$

A simpler, though more approximate, technique that can also be used is to calculate high-dose RBEs from low-dose RBEs using the standard linear-quadratic model,[1,26,27] where the effect of an acute dose of radiation i is assumed to depend on $\alpha_i D_i+\beta D_i^2$. Assuming the validity of this standard linear-quadratic model, it can readily be shown that the RBE, D_j/D_k, of radiation k relative to radiation j, is

$$\mathrm{RBE}(D_k)=\frac{\zeta_j}{2D_k}\left[\sqrt{1+\frac{4}{\zeta_j^2}(\zeta_j\rho_{kj}D_k+D_k^2)}-1\right], \tag{10}$$

where $\zeta_j=\alpha_j/\beta$ and $\rho_{kj}=\alpha_k/\alpha_j$. The ratio ζ_j, i.e., the alpha/beta ratio for the reference radiation, has been repeatedly evaluated; for example, for early responding tissues exposed to megavoltage photons, ζ_j is typically in the range from 8 to 10 Gy.[27] The quantity ρ_{kj} ($=R_k/R_j$, the low-dose RBE) can be calculated from Eq. (6), assuming the corresponding microdosimetric single-event spectra, as well as $w(y)$, are known; it is important to note that the standard linear-quadratic model contained in Eq. (10) does, in fact, contain an implicit assumption that the biological response function, $w(y)$, is proportional to y, which is a reasonable approximation for lineal energy (y) values less than around 100 keV/μm,[21,28] but not necessarily at higher lineal energies, where saturation effects become important.

In summary, measured microdosimetric spectra and the corresponding microdosimetric formalism represent a powerful tool for intercomparing different clinical radiotherapy beams, but at clinical relevant doses, it is generally necessary to take into account in the formalism the fact that cellular targets are subject to a multievent distribution, not just to single events.

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