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Why more needs to be known about RBE effects in modern radiotherapy

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ABSTRACT

Radiation therapy remains a very effective tool in the clinical management and cure of cancer and new techniques of radiation delivery continue to be developed. Of particular note is the growing world-wide interest in particle beam therapy (PBT) using protons or light ions. Such beams (particularly light ions) are associated with an increased relative biological effectiveness (RBE) which, when viewed alongside the more favourable physical distributions of radiation dose available with all forms of particle beams, makes them especially attractive for treating tumours which are associated with disappointing outcomes following conventional X-ray therapy. Although the large body of clinical experience already gained with conventional X-ray therapy will be of paramount importance in guiding the development of treatment programmes using particle beams, understanding and quantification of the RBE effects which are unique to the latter will also be essential. This is because the magnitude of RBE effect is not fixed for any one radiation/tissue combination but is subject to a number of other radiobiological influences. Such relationships may be quantified within the linear–quadratic radiobiological model, within which the associated concept of biologically effective dose (BED) provides a way of inter-comparing the overall biological impact of existing and projected treatments. This paper summarises the main features of RBE and BED, discusses the main quantitative implications for PBT and highlights why clear understanding of RBE effects will be essential to make best use of PBT. It also summarises other clinical applications where knowledge of and allowance for RBE effects is important and suggests that more needs to be done to allow safer practical applications.

1. Introduction

Radiotherapy is of central importance as a cancer treatment modality. A recent European study, quoted by the Royal College of Radiologists (RCR, 2003) found that 49% of tumours which are successfully treated are cured by surgery, 40% by radiotherapy and 11% by chemotherapy. Given the inter-disciplinary nature and technical complexity of radiotherapy the figure of 40% is very respectable and provides a strong indication of why continuing research and investment in this modality is justified. It is also necessary as quality-of-life following poorly executed radiotherapy can be unsatisfactory and, as a consequence, radiation oncologists sometimes have to accept restrictions in tumour dose due to normal tissue constraints.

The most topical advances in radiotherapy are being made in relation to particle beams and there is a rapidly growing World-wide interest in the potential of protons and ion beams for cancer therapy and in assessing the cost-effectiveness arguments with which to justify their use (e.g. Brahme, 2004; Jones, 2006; Lodge et al., 2007). To date around 50,000 patients have been treated with protons and approximately 5000 with carbon ions. Already there are five commercial suppliers of turnkey proton therapy Centres and at least three companies able to supply carbon ion Centres. The use of heavier ions, such as helium and argon, is a possibility for the future.

The common physical feature of proton and ion beams is the existence of the Bragg peak, which allows high doses to be targeted on the tumour with either no dose or very low dose to more distal normal structures (Brahme, 2004). The immediate consequence of this characteristic is an increased Therapeutic Index; relative to conventional (X-ray photon) radiotherapy, with the clear expectation of improved tumour cure with a drastic reduction in normal tissue complications. The likelihood of causing radiation-induced second cancers later in life is also reduced, meaning that protons and ion beams may have a particularly important role in the treatment of childhood cancers (Hall, 2006).

Ion beams and, to a lesser extent, proton beams also possess a radiobiological characteristic which sets them apart from conventional X-rays. They have an increased RBE (relative biological effectiveness) so that, relative to X-rays, less radiation dose is required to produce a given biological effect (Wambersie, 1999).

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For protons the RBE is of the order of 1.1 (Paganetti, 2003), but for carbon ions in the spread-out Bragg peak region the figure is of the order of 3–5 (Weyrather and Kraft, 2004). In the latter case, the high RBE is also associated with a lower dependence on oxygen to effect tumour cell sterilisation and carbon ions may thus be especially effective in treating insensitive and/or radio-resistant tumours (Weyrather and Debus, 2003; Krengli and Orecchia, 2004).

A highly significant feature of the RBE effect is that the RBE values are in fact variable, being dependent on a number of physical and biological influences. This means that RBEs within an irradiated structure are spatially-variant and this has important implications for the efficacy of particle therapy and for the way in which particle beam treatments should be planned. The purpose of this article is to discuss these features of RBE and to outline some of the theoretical modelling work which allows estimation of RBE values in different clinical settings. Given that well over 95% of the clinical experience of radiotherapy has been gained through the use of X-ray beams produced by linear accelerators, quantitative understanding of the more complex radiobiology of particle beams will be an essential requisite to their efficient clinical deployment. A further point, too often overlooked, is that there are a number of examples of where RBE effects are already operative in presently-applied (non-particle beam therapy (PBT)) radiation treatments, thus the ideas discussed here should not be seen as being exclusively relevant to PBT alone.

2. RBE and its influencing factors

For any given biological end-point, the RBE of a test (high-LET) radiation is defined as the ratio of the test dose to that required with the reference (low-LET) radiation, (usually ^{60}Co γ-rays) to achieve that effect, i.e.:

$$\mathrm{RBE} = \frac{d_\mathrm{L}}{d_\mathrm{H}}. \tag{1}$$

Thus, if the required dose with the test radiation is less than the reference dose, RBE > 1. Fig. 1 shows how the RBE concept is interpreted in terms of the differential response characteristics of low- and high-LET cell survival curves. If the basic cell survival curves are described in terms of the linear–quadratic (LQ) model (e.g. Kellerer and Rossi, 1972; Chadwick and Leenhouts, 1973), then surviving fraction (S) as a function of dose (d) at low- and high-LET are, respectively, given as:

$$S_\mathrm{L} = \exp(-\alpha_\mathrm{L} d_\mathrm{L} - \beta_\mathrm{L} d_\mathrm{L}^2), \tag{2}$$

$$S_\mathrm{H} = \exp(-\alpha_\mathrm{H} d_\mathrm{H} - \beta_\mathrm{H} d_\mathrm{H}^2), \tag{3}$$

where the suffixes L and H, respectively, refer to the low- and high-LET instances.

Fig. 2 shows an example of how the RBEs determined at any particular end-point (cell surviving fraction) vary with changing reference dose. The maximum RBE ($\mathrm{RBE_{max}}$) occurs at zero dose and, in terms of microdosimetric theory (Kellerer and Rossi, 1972; Dale and Jones, 1999), corresponds to the ratio between the respective high- and low-LET linear radiosensitivity constants, α_H and α_L, i.e.:

$$\mathrm{RBE_{max}} = \frac{\alpha_\mathrm{H}}{\alpha_\mathrm{L}}. \tag{4}$$

If the quadratic radiosensitivity coefficients (β_H and β_L) are unchanged with changing LET (i.e. ($\beta_\mathrm{H} = \beta_\mathrm{L}$) then, at large doses, the RBE tends to unity. However, this constancy of β, assumed by the theory of Kellerer and Rossi (1972), has been challenged (Goodhead, 1977) and, if β does change with LET, then RBE will tend asymptotically to an alternative minimum value ($\mathrm{RBE_{min}}$) given by:

$$\mathrm{RBE_{min}} = \sqrt{\frac{\beta_\mathrm{H}}{\beta_\mathrm{L}}}, \tag{5}$$

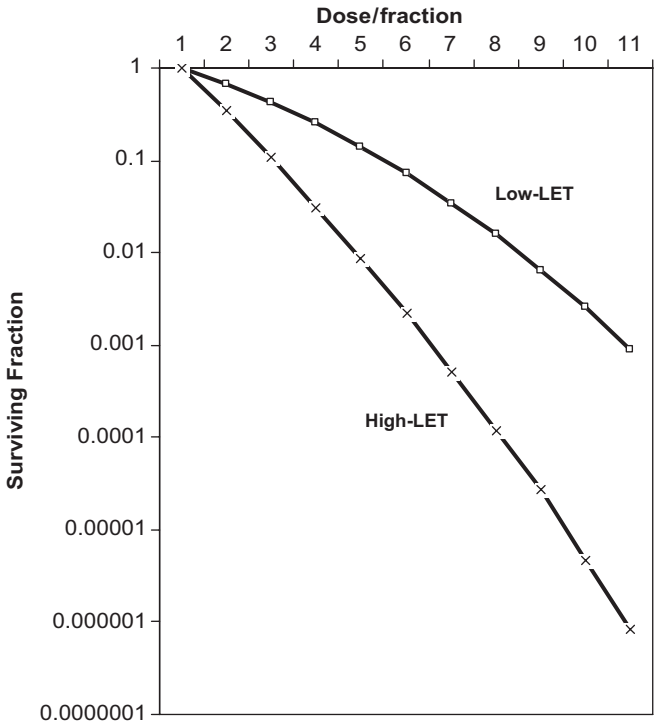

Fig. 1. Schematic showing the different response of a cell line to irradiation with low- and high-LET radiation. The RBE at any given end-point (surviving fraction) is the ratio of the respective low- to high-LET doses required to attain the survival (Eq. (1)).

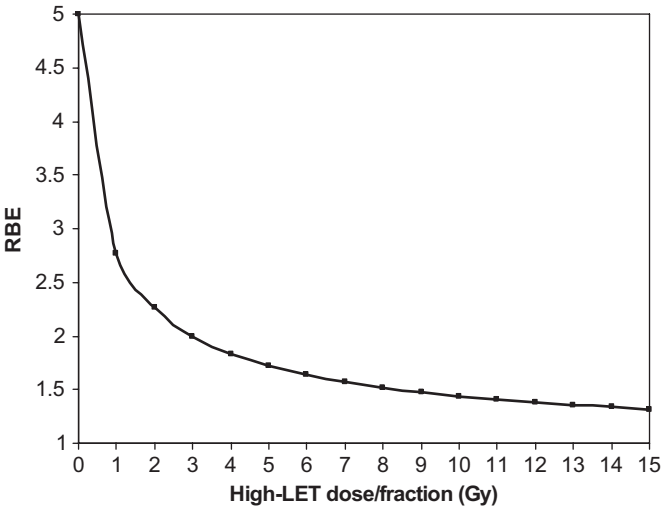

Fig. 2. Variation of RBE with high-LET dose per fraction derived using Eq. (6b) from data of the type shown in Fig. 1. The maximum RBE ($\mathrm{RBE_{max}}$) is assumed here to be 5 and $\mathrm{RBE_{min}}$ is set to unity, which is the asymptotic value of RBE. As shown in Fig. 3, other $\mathrm{RBE_{min}}$ values will influence the rate of change of RBE with changing dose per fraction. The assumed low-LET α/β value is 3 Gy.