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RBE of ion beams in hypofractionated radiotherapy (SBRT)

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ABSTRACT

An important advantage for the application of carbon ion beams in tumour therapy is their increased relative biological effectiveness (RBE) as compared to conventional photon radiation. Since RBE among other factors depends on the dose level, the precise knowledge of the RBE dependence on the dose is of particular importance for the comparison of different fractionation schemes, involving different doses per fraction. Here we describe some general properties of the RBE vs. dose dependence, which are determined using a simple modelling approach based on the linear-quadratic model as well as a more sophisticated predictive model for the description of RBE. We show that for both approaches the systematic dependence of RBE on the cell or tissue type as characterized by the α/β-ratio of the photon linear quadratic parameters is expected to be inverted at high doses as compared to low doses.

We demonstrate that this inversion is not a model specific feature, but a rather generic feature resulting from the linear-quadratic shape of dose response curves and the correlation between RBE and the photon α/β-ratio. The results are discussed with respect to other modelling approaches and to their implications for clinical applications of carbon ion beams using hypofractionated treatment schedules.

1. Introduction

Ion beams exhibit physical as well as biological advantages in applications for radiotherapy as compared to conventional photon beams. The physical advantages are characterized by a better dose conformation to the tumour as a consequence of the inverted depth dose profile, and ions heavier than protons in addition show a less pronounced scattering. One of the potential biological advantages of heavier ions like e.g. carbon ions is the significantly increased relative biological effectiveness (RBE) particularly in the Bragg peak region, i.e. in the part of the depth dose profile that is located in the clinical target volume covering the tumour.

The increased RBE has to be taken into account in treatment planning in order to choose the appropriate prescribed dose for the patient treatments. However, RBE is not represented by a single, constant number, but depends in a complex manner on physical and biological parameters. It depends e.g. on the particle species, ion beam energy, LET, dose and the cell or tissue type under consideration. The full consideration of all these dependencies in general requires the use of biophysical models that are able to predict the RBE with sufficient accuracy [1–3].

Since hypofractionated treatment schedules become increasingly important in ion beam therapy [4,5], the accurate description and understanding of the RBE dependence on dose is of particular interest for treatment planning. In general, a decrease of RBE with increasing dose is observed and the RBE approaches a small value typically between 1 and 2 in the case of very high doses [6]. For the clinical application the exact shape of the dose dependence and its connection to the cell and tissue type dependence are of particular concern. Typically, RBE_{α} values (representing the RBE value for the initial slope of dose effect curves) for cells or tissues characterized by a small α/β ratio after photon radiation are higher compared to those characterized by a high α/β ratio after photon radiation [7].

In a first naive assumption one could then expect that towards higher doses always the same order should be preserved, i.e. cells and tissues with high α/β ratio should for all doses exhibit a smaller RBE than those with a small α/β ratio. In this simple view, it would be expected that the RBE(D) curves never cross.

However, based on a linear-quadratic parameterization of dose–response curves for photon and high-LET radiation, it has been shown e.g. by Dale et al. [9] that towards high doses the order of the curves might be reverted under certain conditions. In their approach, however, RBE values are completely decoupled from the photon-LQ parameters. We here thus analyze in more detail the predictions of the Local Effect Model (LEM) [2,8], which uses the

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photon dose response curve to predict the high-LET dose response curve. According to that approach, the corresponding RBE values are strongly correlated with the photon LQ parameters. In this contribution we thus investigate the dose dependence of RBE as relevant for hypofractionated regimens with respect to the α/β ratio. We first analyze the RBE(D) dependence using a simple LQ-based approach, taking into account the correlation between RBE_α and the photon α/β-ratio. We then present the LEM predictions and compare these with our LQ-based approach and with the results reported by Dale et al. [9].

2. Methods

We analyze the dose dependence of RBE exemplarily for the case of carbon ions at an LET of 77 keV/µm. This choice is an idealized representative for a clinical carbon Bragg peak in the target volume, although it neglects the mixed LET and particle species distribution of a real extended Bragg peak applied in the clinics. The analysis is performed for three tissue types, reflected by *photon* α/β ratios of 2, 10.5 and 27.5 Gy. This range of α/β ratios covers the observed range for tumours and normal tissues and for both in-vitro and in-vivo or clinical responses. However, we do not make any specific assumptions about the association between α/β-ratios and tumour or normal tissues. To predict the course of RBE with dose we apply two models. First the linear quadratic (LQ) approach is used in combination with adequate low-LET and high-LET LQ parameters. This rather empirical approach bases on a minimum amount of assumptions. Its prediction will be compared with the LEM IV model [2,8], that is designed and validated for predicting RBE values for clinical purposes. The LEM predicts RBE values from the photon dose response curve of a cell or tissue under consideration, which is parameterized according to a modified LQ model which is characterized by a transition to a linear shape at high doses (the so called linear quadratic- linear (LQL) model). Thus we compare here a very simple and basic model with a state of the art RBE model.

2.1. Linear-quadratic approach

The linear quadratic model is used since a long time to parameterize dose response curves after both photon and ion irradiation. It allows to solve for the doses needed for a given effect and thus the RBE can directly be evaluated, provided the LQ parameters for both photon and ion dose response are known [9]. In its simplest application two additional assumptions are made, that are frequently used also for other analyses namely that radiation quality affects only the linear coefficient α, whereas the quadratic coefficient β is assumed to be constant in a first approximation, i.e. $\beta_I = \beta_\gamma = \beta$. Then the dose–response curves for photon and ion beam irradiation are given by:

$$S(D_\gamma) = e^{-(\alpha_\gamma D_\gamma + \beta D_\gamma^2)} \quad (1)$$

$$S(D_I) = e^{-(\alpha_I D_I + \beta D_I^2)} = e^{-(RBE_\alpha \alpha_\gamma D_I + \beta D_I^2)} \quad (2)$$

Radiation quality is then fully characterized by $RBE_\alpha = \alpha_I/\alpha_\gamma$, representing the RBE for the initial slope of the dose response curves. The values for RBE_α can be measured or inferred by any model. For the adequate choice of RBE_α, we make use here of the known correlation between RBE_α and the photon α/β-ratio, which can be directly derived from experimental data and that is also consistently described by the LEM. Consequently, the α_I values and with that the RBE_α values chosen here are identical to those predicted by the LEM in the way described below so that for both models the curves for RBE(D) start at the same RBE value for $D = 0$.

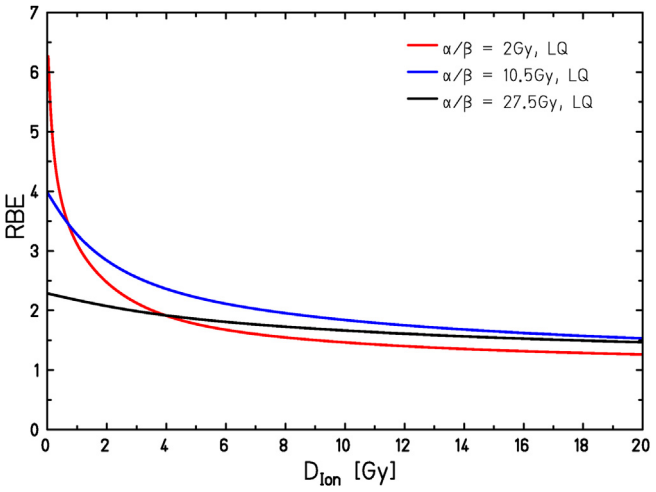

Figure 1. Dose dependence of RBE for three different tissue characteristics as predicted by the simple linear-quadratic approach. Input paramters α_γ, α_I and β_γ see Table 1.

Potential differences of the models should then become visible as different shapes of the RBE(D) curves.

2.2. Biophysical modelling of RBE using the LEM

The LEM is based on the assumption that the DNA damage induced locally at a given position in the track of a particle traversing the cell nucleus is only determined by the local dose at this position. The local dose is defined by the expectation value of the energy release at a given distance from the particle trajectory. In combination with the known response of a biological object to conventional photon radiation it allows predicting the response to ion beam irradiation [2,8]. The LEM thus allows determining RBE values for a given combination of ion beams and cells or tissues and for arbitrary dose values. Based on this model, it has been shown that the above mentioned assumption of a constant β for all radiation qualities is an oversimplification [8]. A second difference compared to the simplistic LQ approach is, that within the LEM the photon dose response curve is described in terms of the LQL model which accounts for deviations from the pure linear-quadratic model towards higher doses. The LEM predictions thus require an additional parameter D_t, which characterizes the transition of the photon dose response curve from a linear-quadratic shape to a purely linear shape for $D > D_t$. As described e.g. by Astrahan [10] and Friedrich et al. [7], the corresponding value of D_t can be expected to increase linearly with the α/β-ratio; for the calculations shown here we have assumed as a first approximation a simple scaling relationship of $D_t = 2.85 \times \alpha/\beta$, which seems to be suitable for in-vivo endpoints.

The high LET dose response is calculated for discrete dose points by means of a Monte Carlo approach taking into account the spatial distribution of ion hits on cell nuclei ("full simulation", see Ref. [8]). Although the ion dose response curve does not necessarily follow a simple parameterization, in general it can be represented also with sufficient accuracy within the LQL formalism. It is thus of particular interest whether the conceptual differences between the LQ-approach using a constant β and LEM-approach allowing for a variable β will result in different shapes of the RBE(D) dependence at high doses.

3. Results

The expected dose dependence of the RBE calculated on the basis of Eqs. (1) and (2) for three different tissue characteristics,