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**CALCULATION OF RBE FOR NORMAL TISSUE
COMPLICATIONS BASED ON CHARGED PARTICLE TRACK
STRUCTURE**

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Calculation of RBE for normal tissue complications
based on charged particle track structure

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Abstract

A new approach for the calculation of RBE for normal tissue complications after charged particle and neutron irradiation is discussed. It is based on the extension of a model originally developed for the application to cell survival. It can be shown, that according to the model RBE values are determined largely by the α/β -ratio of the photon dose response curve, but are expected to be nearly independent of the absolute values of α and β . Thus, the model can be applied to normal tissue complications as well, where α/β -ratios can be determined by means of fractionation experiments. Agreement of model predictions and experimental results obtained in animal experiments confirm the applicability of the model even in the case of complex biological endpoints.

Dans ce travail un nouveau traitement est discuté pour le calcul de RBE concernant les complications dans le tissu sain après l'irradiation avec des particules chargées et des neutrons. La base de ces estimations est l'extention d'un modèle développé d'abord pour la description de la survie cellulaire. Selon ce modèle les valeurs de RBE sont largement déterminées par le quotient α/β descendu des courbes de réponse en fonction de la dose photon, mais presque indépendant des valeurs absolues de α et β . Par conséquent une application de ce modèle sur les complications de tissu sain est réalisée par détermination du quotient α/β à l'aide des valeurs moyennes obtenues à partir des expériences fractionnées. La concordance des estimations du modèle avec les résultats expérimentaux obtenu par des expériences avec des animaux a confirmé une application même au cas des points finals plus compliqués.

Keywords

RBE, normal tissue complication, track structure, model calculation

Introduction

Tumor doses in radiation therapy are limited by normal tissue complications in general. For the optimal application of new and promising treatment modalities like charged particle beams, the increased biological efficiency of these beams has to be taken into account when estimating normal tissue tolerance doses as well as tumor doses. Although highest RBE values are expected in the extended Bragg peak region and thus in the tumor volume, slightly increased RBE are reported as well for normal tissue reactions in the entrance channel.

Up to now, mainly cellular and animal radiobiological experiments are used to estimate clinically relevant RBE values. Because of the better statistics and correspondingly higher accuracy, cellular experiments are more appropriate to study the general systematics of RBE as a function of radiation quality. In contrast, animal studies are advantageous because they are more closely related to the clinical situation.

As a complement to the cellular and animal studies, we have developed an additional approach based on model calculations for the determination of RBE values for applications to heavy ion therapy. The model calculations were first applied to cell survival studies and are based on the knowledge of the local, microscopic dose distribution and the photon dose effect curve [6,7,8]. However, we could show, that the model can be applied to more complex endpoints like normal tissue complication probabilities without major modifications.

This paper briefly summarizes the main aspects of the model when applied to cellular survival and then focuses on the implications of the model for a generalization to other endpoints. A comparison of model predictions with experimental data for neutron irradiation will be presented as well and discussed in view of applications to heavy ion tumor therapy.

Materials and Methods

The model calculations are based on three sets of input data: the X-ray dose effect curve $S_X(D)$, the radial dose distribution $D(r)$ inside the charged particle tracks and the size of the critical target. When applied to mammalian cell survival, the log of survival $\ln S$ is taken as a descriptor of the biological effect, and the critical target is assumed to be the cell nucleus. In accordance with theoretical and experimental investigations, the radial dose distribution inside the track is assumed to follow a $1/r^2$ -law [5].

The survival probability for an individual cell is calculated to be

$$S_{Ion} = e^{-N_{lethal}}, \quad (1)$$

where N_{lethal} , the average number of lethal events, is given by

$$N_{lethal} = \int_x \int_y \int_z \frac{-\ln S_X(D(x,y,z))}{V} dx dy dz. \quad (2)$$

$D(x,y,z)$ denotes the actual local dose deposited in the critical target at position (x,y,z) defined by the sum of local doses from all tracks contributing to this specific location, and V is the volume of the critical target, the cell nucleus. Monte Carlo methods are

used to simulate the spatial distribution of particle traversals. Survival of a population is determined as the average survival probability of the individual cells.

The most remarkable feature of eq. (2) is, that it is based on measurable quantities only and that no free parameters are introduced. It predicts the increased biological efficiency of charged particles solely from their different spatial dose distribution compared to photons.

The model is able to reproduce several high LET specific features like increased RBE, the shift of the RBE maximum as a function of the atomic number and the complex pattern of inactivation probabilities when plotted as a function of LET over the whole range from 2 to 15000 $keV\mu m$. Comparison of the model predictions and experimental results obtained for track segment conditions (defined energy and LET) are discussed in more detail in [8]. Here, we will focus on aspects of more complex radiation fields like superimposed Bragg peaks, as they are applied in charged particle therapy, or like the field of secondary charged particles produced by neutrons. Due to the more complex fields compared to track segment conditions, some approximations have to be applied to the calculations, which however do not touch the general concepts as described previously and will be discussed in more detail in a separate paper.

One important consequence of eq. (2) is, that an increased efficiency of charged particles is only predicted in the case of shouldered photon dose effect curves. For linear dose effect curves, $\ln S_X(D) = \alpha D$, so that the order of multiplication by the constant α and integration can be interchanged. Then, eq. (2) becomes equivalent to a simple averaging of the dose and thus N_{lethal} is independent on the spatial distribution of energy depositions. If, however, dose response curves are shouldered, high local doses contribute with a higher weight and thus concentration of the energy deposition leads to a higher efficiency.

As a consequence, the RBE is expected to depend on the shape of the shoulder, consistent with experimental findings, that highest RBE values are found in the case of large shoulders for the photon dose effect curve in general. This is demonstrated in Fig. 1, where on the left side model calculations for a given ratio α_X/β_X , but different absolute values of α_X and β_X are shown. In contrast, Fig. 1b represents a series of calculations for fixed α_X , but different ratios α_X/β_X . In the case of constant α_X/β_X RBE values are nearly independent on the absolute values of α and β , although these values vary by a factor of 50, whereas RBE varies significantly, when the ratio is changed ¹. Thus, it can be concluded, that the knowledge of the general shape and width of the shoulder of the photon dose effect curve appears to be sufficient to estimate RBE values even if the absolute dose effect curve is not known.

This opens a wide field of applications for the model in particular in the case of more complex tissue endpoints. For example, for normal tissue complications survival curves for the target cells are not available in general, and the correlation between cell survival and the the observed endpoints remains unclear. However, α_X/β_X -ratios can be obtained from fractionation experiments for the endpoint under consideration according to the method of Douglas and Fowler [2]. On the basis of these ratios RBE values can then be estimated

¹It has to be noted, that the shape of X-ray survival curves is assumed to be shouldered with a purely exponential tail, as seen in most experiments. Therefore, the linear quadratic approach is only valid for low and medium doses, whereas for high doses, $D > D_{cut}$, a linear term is used. The threshold dose D_{cut} has been chosen the same for all cases shown in Fig. 1a and 1b.

without explicitly referring to survival curves of the corresponding target cells. Instead, a hypothetical survival curve is reconstructed from the known α_X/β_X -ratio by choosing an arbitrary value for α situated in the mid range of typically observed experimental values. β is then defined by the given ratio, and thus a complete dose effect curve can be reconstructed and used as input for the model, as it was developed for calculation of cellular survival.

Although the target for the induction of tissue complications is not as well defined as for cellular survival, it has been chosen as the cell nuclei of the tissue under consideration. However, the target size used as input for the model is most relevant only for very high LET and thus at the end of the particle range of heavier particles. It has only minor influence in the case of lower LET and correspondingly higher particle fluences in the entrance channel of charged particle beams, for example.

It has to be pointed out, that the model is based on photon input data as close as possible to the tissue endpoint under investigation, which represents an important feature when dealing with treatment planning. In the following, a comparison of model predictions according to the method described above with experimental data will be discussed.

Results

Fig. 2 and 3 compare the model predictions and experimental results for two different experimental systems: the neutron irradiation of the rat spinal cord and the mouse skin. In each figure, the total dose required to obtain the desired endpoint (a) and the resulting RBE as a function of the photon dose per fraction are shown (b). The α_X/β_X -ratios used as input for the calculation were obtained from a fit to the Douglas-Fowler plot of the low LET fractionation data as given in the literature. The calculation of fractionation effects after neutron irradiation is based on the assumption, that no repopulation occurs and repair is completed within the fractionation interval. Since charged particle spectra for neutron irradiation were not available for all incident neutron energies, the calculations had to be performed for slightly different energies compared to the experimental data. In addition, the charged particle spectra were based on the assumption of monoenergetic incident neutrons. Despite these small differences, a good agreement between model calculations and experimental results is observed for the induction of ataxia in rats and for mouse skin desquamation in particular for low energies. For higher energies, deviations are larger, but the main features as e.g. the decrease of RBE with increasing neutron energy and increase of RBE with decreasing dose per fraction are predicted well by the model.

Discussion

The agreement between model calculations and experimental data as shown in the previous section suggests, that even in the case of quite complex biological endpoints like normal tissue complications the increased biological efficiency of high LET beams can be traced back to the different spatial energy deposition pattern of photons and charged particles.

In addition to the spatial differences in the energy deposition, the low LET dose response plays a key role for the calculation, because the shoulder of the dose response curve determines the maximal RBE which can be expected. By referring to the low LET dose response, the model is able to reflect the broad variability of RBE values depending on the biological endpoint under consideration. This is in contrast to other models, which mainly focus on the physical differences in the stochastics of energy depositions as e.g. the microdosimetric approach.

Because the model calculations can be adopted easily for any given charged particle radiation field, they will be helpful in systematic investigations for the optimization of the treatment modalities. Therefore, they will help to reduce the efforts required for cellular and animal radiobiological experiments. However, a certain set of data is urgently needed to test the model calculations.

With respect to these checks, the experience obtained with neutrons on the cellular and animal level represents an invaluable data base. Thus, before the model will be applied to heavy ion treatment planning, it will be extensively tested by means of the neutron data. Here, it will be even possible to check the predictions for the clinical case.

A first application of the treatment planning based on this model has been tested already in the framework of animal experiments in preparation of the heavy ion therapy project at GSI. Normal tissue complications in the skin and lung of minipigs were investigated using a carbon beam. The model was used to calculate the carbon doses, which were isoeffective to the photon doses which were applied in parallel. The early skin reaction analysed up to now actually confirms the isoeffectiveness and thus supports the applicability of the model [9].

In conclusion, we have shown, that our model based on the microscopic dose distribution and the low LET response is able to predict biological effects of high LET radiation on the cellular level as well as on more complex endpoints like normal tissue complications. The general agreement of model predictions and experimental results supports the assumption, that it can be applied for the estimation of clinically relevant RBE values as well.

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Figure legends

Figure 1

Correlation of RBE with the α/β -ratio as predicted by the model. Calculations were performed for 14 MeV monoenergetic neutrons; corresponding secondary charged particle spectra were taken from [1].

(a): RBE as function of photon dose for three different sets of α and β , varying by a factor of 50, but with the same ratio. (b): RBE as function of photon dose for $\alpha = 0.1$ and three different β values.

Figure 2

Comparison of model calculations and experimental results for neutron irradiation of the rat spinal cord. The induction of ataxia in 50% of the animals was chosen as endpoint. Experimental data were taken from Hornsey [3]. Calculations were based on $\alpha/\beta=6.6$ as determined from a fit of the Douglas-Fowler plot of the photon data.

(a): Total dose as a function of fraction number; (b): corresponding RBE as function of the photon dose per fraction.

Figure 3

Comparison of model calculations and experimental results for the induction of skin desquamation after neutron irradiation of the mouse skin. A skin scoring level of 1.5 was chosen as endpoint. Experimental data were taken from Joiner et al. [4]. Calculations were based on $\alpha/\beta=8.6$ as given in [4].

(a): Total dose as a function of fraction number; (b): corresponding RBE as function of the photon dose per fraction.

Figure 1:

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Figure 2:

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Figure 3:

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