Int. J. Radiation Oncology Biol. Phys., Vol. 71, No. 3, pp. 866–872, 2008

0360-3016/08/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2008.02.037

BIOLOGY CONTRIBUTION

ACCURACY OF THE LOCAL EFFECT MODEL FOR THE PREDICTION OF BIOLOGIC EFFECTS OF CARBON ION BEAMS *IN VITRO* AND *IN VIVO*

THILO ELSÄSSER, PH.D., MICHAEL KRÄMER, PH.D., AND MICHAEL SCHOLZ, PH.D.

Department of Biophysics, Gesellschaft für Schwerionenforschung, Darmstadt, Germany

Purpose: To analyze the accuracy of relative biologic effectiveness (RBE) values for treatment planning in carbon ion radiotherapy based on the local effect model (LEM) and to discuss the implications on the clinically relevant depth dose profiles.

Methods and Materials: Predictions of the LEM are compared with a broad panel of experimental data *in vitro* and to the tolerance of the rat spinal cord *in vivo*. To improve the accuracy of the LEM, the description of track structure is modified by taking into account a velocity-dependent extension of the inner part of the track.

Results: The original version of the LEM (LEM I) underestimates the therapeutic ratio of carbon ions (i.e., the ratio of RBE in the Bragg peak region as compared with the RBE in the entrance channel). Although significantly reduced, the cluster extension of the LEM (LEM II) still shows the same tendency. Implementation of the modified track structure (LEM III) almost completely compensates these systematic deviations, and predictions of RBE by LEM III for high and low energetic carbon ions show good agreement for a wide panel of different cell lines, as well as for the tolerance of the rat spinal cord. As a consequence, the expected RBE in the normal tissue surrounding the tumor becomes significantly lower than estimated with the LEM in its original version (LEM I).

Conclusions: The modified track structure description represents an empiric approach to improve the accuracy of the LEM for treatment planning. This will be particularly useful for further optimization of carbon ion therapy in general and with respect to comparison with other treatment modalities, such as protons or intensity-modulated radiotherapy.

Charged particle radiotherapy, Carbon ions, Treatment planning, Radiation tolerance, Rat spinal cord, Relative biologic effectiveness (RBE).

INTRODUCTION

There is rapidly growing interest worldwide in carbon ion beam therapy. This is due to the excellent clinical results (1–3) based on the advantageous depth dose profile of ion beams as well as due to their favorable radiobiologic properties, namely their increase in relative biologic effectiveness (RBE) toward the end of their range. As has been shown in numerous experiments *in vivo* and *in vitro*, the RBE depends on physical factors, such as ion species, beam energy, and dose level, and on biologic factors, such as the cell or tissue type under consideration (4–8). Because of the complex dependencies of RBE, biophysical models play a key role for the estimation of clinically relevant RBE values in treatment planning. For the pilot project at the Gesellschaft für Schwerionenforschung (GSI), the local effect model (LEM) was developed as the first model for treatment planning that takes these complex dependencies into account. The version currently implemented in the treatment-planning procedure (9) (called ''LEM I'' here) was published in 1997, and although certain limitations of the model became obvious in the following years, it has not been replaced, to allow the direct comparability of the clinical trials over the entire period of the pilot project. This is particularly reasonable because the deviations between model prediction and experimental data were such that the model tends to overestimate the effective dose in the entrance channel and to slightly underestimate the effect in the tumor region. This became visible, for example, in experiments performed for biologic verification of treatment plans *in vitro* (10) as well as in experiments investigating the tolerance of the rat spinal cord *in vivo* (11). However, from a clinical point of view these deviations were on the ''safe side'' for the patients, in the sense that according to the method described above the actually expected effects in the normal tissue surrounding the tumor should be lower than predicted by the model, whereas tumor control could actually be somewhat higher.

In recent years, we have been investigating possible improvements to achieve better agreement between model

Reprint requests to: Michael Scholz, Ph.D., Department of Biophysics, Gesellschaft für Schwerionenforschung, Planckstrasse 1, D-64291 Darmstadt, Germany. Tel: (+49) 6159-71-1340; Fax: (+49) 6159-71-2106; E-mail: m.scholz@gsi.de

Conflict of interest: none.

Acknowledgment—The authors thank Michael Kreim and Till Böhlen for their computational assistance with data analysis.

Received Sept 25, 2007, and in revised form Feb 7, 2008. Accepted for publication Feb 25, 2008.

predictions and experimental data. A first important step has been achieved by including effects of clustered damages (12). This extension of the model (called ''LEM II'' here) showed a significant improvement for particles with lower LET (i.e., for lighter ions like helium in general and for heavier ions like carbon specifically for high energies).

In the first part of the present report we compare the RBE values for the (published) different LEM model versions (LEM I and II) with a broad panel of different cell lines *in vitro*, to achieve a quantitative measure for the agreement between model prediction and experimental data. Although the systematic differences are significantly reduced with the cluster extension of the LEM, they still show a similar tendency as the original version of the LEM. Therefore, we discuss possible further improvements and the implications of such improvements on the prediction of effective depth dose profiles in a typical clinical setting.

METHODS AND MATERIALS

Details of the LEM are reported elsewhere (9, 12), and only the essential features of the model are briefly summarized here. The principal assumption for all versions of the LEM is that the local biologic effect (i.e., the biologic damage in a small subvolume of the cell nucleus) is solely determined by the expected value of the energy deposition in that subvolume and is independent of the particular radiation type leading to that energy deposition. This principle allows deriving the effects of particle radiation from the effects observed for conventional photon radiation. For a given biologic object, all the differences in the biologic action of charged particle beams are thus attributed to the different spatial energy deposition pattern of charged particles compared with photon irradiation (i.e., on track structure). Furthermore, for a given radiation type, any difference in RBE between different cells or tissue types should correspond to a difference in the photon dose–response curve.

The energy deposition pattern of charged particles (i.e., the track structure) is determined essentially by the secondary electrons (δ-electrons) liberated by the primary particle when penetrating matter. According to experimental data and in line with theoretical considerations about the transport of secondary electrons, the average energy deposition D as a function of the distance r from the trajectory, the radial dose profile, follows an $1/r^2$ dependence for distances above a few nanometers up to a maximum value of the track diameter. For the inner part of the track, a constant local dose is assumed:

$$D(r) = \begin{cases} \lambda\ LET/r_{\min}^2 & : \quad r < r_{\min} \\ \lambda\ LET/r^2 & : r_{\min} \le r \le r_{\max} \\ 0 & : \quad r > r_{\max} \end{cases} \tag{1}$$

where *LET* denotes the linear energy transfer and λ is a normalization constant to ensure that the radial integral reproduces the LET. All LET values given in this article refer to the unrestricted LET_∞; for simplicity, however, the index ''∞'' is omitted in the following. The parameter $r_{\min}$ describes the transition from the dose plateau in the track center to the $1/r^2$ behavior, and $r_{\max}$ is the maximum radius determined by the δ-electrons with the highest energy. This track radius $r_{\max}$ can be parameterized using a power law of the form (13)

$$r_{\max} = \gamma E^{\delta};\ \gamma = 0.062\ \mu m\ (MeV/u)^{-1.7},\ \delta = 1.7 \tag{2}$$

where E is the specific energy of the projectile, and γ represents the track diameter for a specific energy of 1 MeV/u.

The value of $r_{\min}$ was set to 10 nm in the original implementation LEM I (9); this comparably large value takes into account in a rough approximation the diffusion of biologically reactive radicals. For the cluster extension (LEM II), a more realistic description is used based on $r_{\min} = 0.3$ nm. In that case, diffusion of biologically reactive radicals is explicitly modeled on the basis of a Gaussian shaped profile with $\sigma = 4$ nm (12), representing the typical diffusion length in a cellular environment.

Given the accumulated local dose distribution according to the impact parameters of a given set of impinging ions, the average number of lethal events induced per cell by heavy ion irradiation can then be obtained by integration of the local density $\nu(d(x,y,z))$ for the production of lethal events, which is assumed to be identical for ion and photon irradiation:

$$\overline{N_{I,Ion}} = \int \nu(d(x,y,z))\ dV_{Nucleus} = \int \frac{-\log S_X(d(x,y,z))}{V_{Nucleus}}\ dV_{Nucleus} \tag{3}$$

where $S_X(d)$ denotes the photon dose–response curve. This formula clearly demonstrates the theoretical link between the biologic effect of photon radiation and ion radiation. The integrand is completely determined by the low-LET response of the object under investigation; the particle effect is ''hidden'' in the inhomogeneous local dose distribution $d(x,y,z)$. For a given pattern of particle traversals, the ion survival probability S_{Ion} for a cell is then given by

$$S_{Ion} = e^{-\overline{N_{I,Ion}}} \tag{4}$$

Equation 3 is the most general formulation of the LEM; it does not rely on any particular representation of the photon dose–response curve; it can be applied even if only numeric values of $S_X(D)$ are available. For practical reasons, we take the linear-quadratic approach for the description of the low-LET dose–response curve. However, a modified version of the linear-quadratic approach is used, because for many biologic objects a transition from the shouldered to a more exponential shape of the dose–response curve is observed at high doses. This transition is described by a parameter D_t, representing the transition dose to the exponential shape with slope $s_{\max} = \alpha + 2\beta D_t$, so that the dose response is finally given by

$$S_X(D) = \begin{cases} e^{-(\alpha_X D + \beta_X D^2)} & : D \le D_t \\ e^{-(\alpha_X D_t + \beta_X D_t^2 + s_{\max}(D - D_t))} & : D > D_t \end{cases} \tag{5}$$

Although in principle D_t represents a measurable quantity, in general the dose D_t cannot be directly derived from experimental data, because survival curves can be measured only down to a survival of 10^{-3} for most mammalian cell lines.

The calculation of the biologic effects for treatment planning according to Eq. 3 requires unacceptable computing times; approximations have thus been introduced to drastically increase the computational speed without significant loss of precision (9, 14, 15) for doses typically used in carbon ion therapy. Application of the model to biologic endpoints *in vivo* follows the same scheme as described above; however, the linear-quadratic parameters of the photon dose–response curve for the endpoint *in vivo* is used as input instead of the cellular survival parameters (16).

Recently, an improved version (LEM II) has been described (12), which takes into account in more detail the clusters of damage induced by the high local doses within the charged particle tracks. Based on the probability to induce double-strand breaks from combinations of neighboring single-strand breaks, this improved version of the model allows one to better predict the decrease of RBE toward