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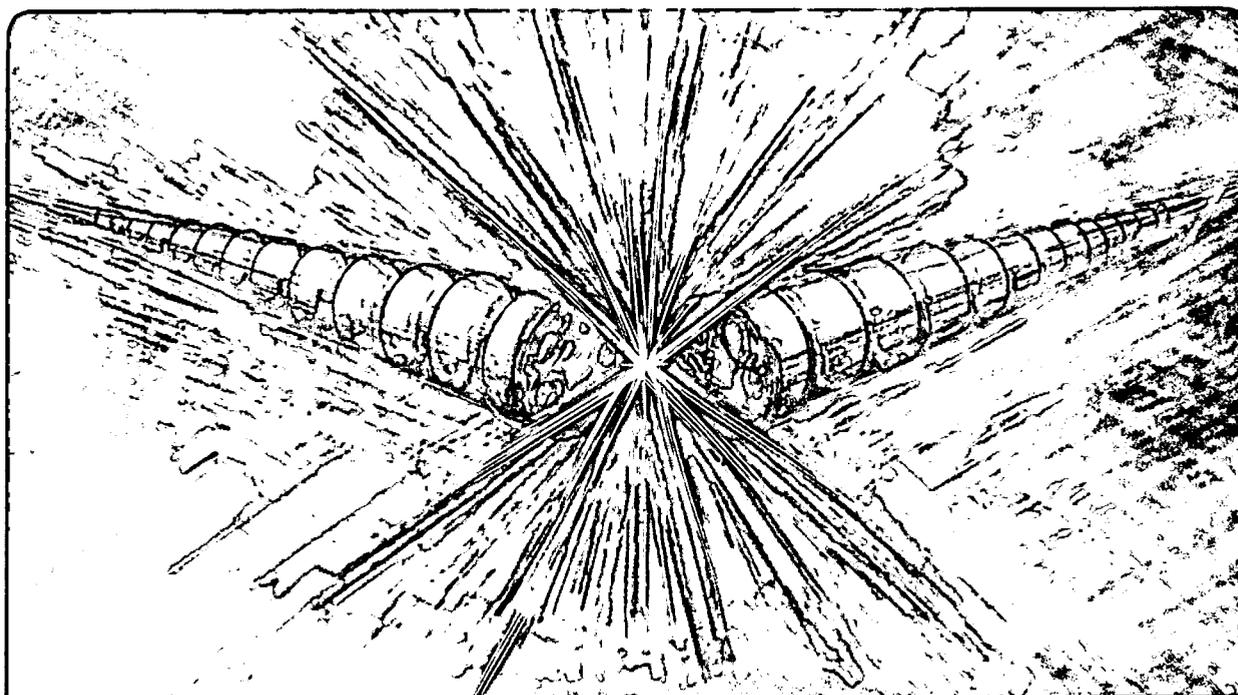
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Calculating Survival Curves in Spread-peaks of Heavy Ion Beams and Comparison with Experiment

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Introduction

In preparing for treating patients with high-energy ion beams, it is important first to determine the composition of the beam, that is, the relative mixes of the various primary and secondary particles and their LET spectra, and secondly to estimate the cell killing expected during a treatment schedule. This requires measurements of the beam composition at various depths through the spread-peak region, and a calculation of cell survival using a cell-killing model designed to accommodate the mixed LET nature of the beam in the spread-peak region. This talk presents results of an experiment in which a particle identification telescope, the BERKLET, was used to measure the LET spectra of the primary and secondary particles at two positions in a 12-cm-spread-peak of a 585 MeV/amu neon ion beam at the Bevalac. Cell survival measurements were made at the same positions at which the LET-spectra were measured. The survival curves obtained were compared with calculations using the LPL (Lethal, Potentially Lethal) model of cell-killing. Results agree quite well at doses up to about 4 Gy. A quantity proportional to the RBE at 10% survival, when plotted against dose-averaged LET for a number of different beams and energies, appears to be a fairly good predictor of biological effect. This would not be expected if the difference in biological effect due to differences in track structure between various ions at the same LET played a significant role in modifying cell-killing in the range of LETs covered by this experiment.

The Physical Measurements

The LET spectra were measured by the BERKLET (Llacer *et al.*, 1989). Briefly, the BERKLET consists of a 400- μm -thick silicon detector followed by a germanium detector 5.5 cm in depth corresponding to a water equivalent depth of 18.5 cm. These detectors in coincidence provide information on dE/dx (ΔE in the silicon) and residual range (in the germanium) for stopping particles so that individual particles can be identified by their charge and dE/dx . The device is shown in Fig. 1.

The beam used for these experiments was a neon ion beam with an initial energy of 585 MeV/amu. A bar ridge filter spread the Bragg peak region of the beam to 12 cm. The measurements were made in the "proximal peak", defined as 1 cm downstream of the start of the stopping region, and in the "distal peak", defined as 1 cm upstream of the end of the stopping region. These positions are indicated on the Bragg curve for the 585 MeV/amu neon beam shown in Fig. 2.

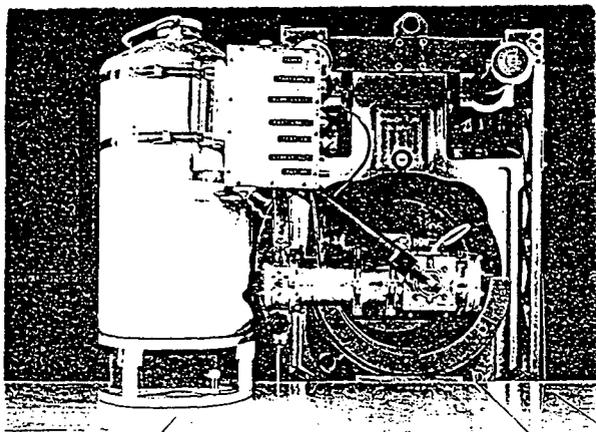


Fig. 1. The BERKLET particle identification telescope.

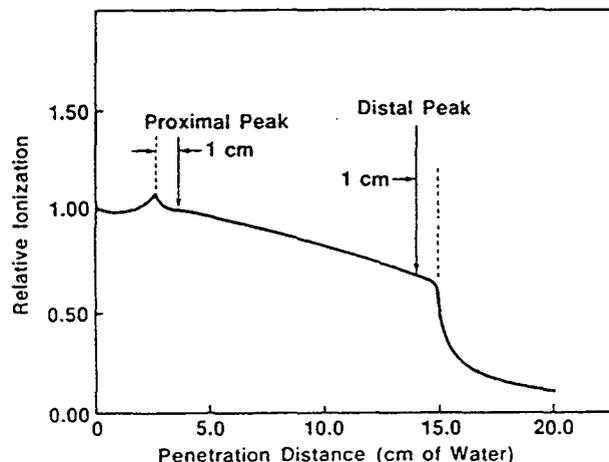


Fig. 2. The Bragg ionization curve for a 585 MeV/amu neon ion beam spread to 12 cm by a bar ridge filter. The proximal and distal peak positions are defined.

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The Lethal Potentially Lethal (LPL) Model of Cell Killing

The survival expression for the Lethal Potentially Lethal Model is given as (Curtis, 1986):

$$S = \exp[-(\eta_L + \eta_{PL})D] \left[1 + \frac{T}{\epsilon} \eta_{PL} D\right]^\epsilon \quad (1)$$

Here $\eta_L D$ and $\eta_{PL} D$ are the number of lethal and potentially lethal lesions, respectively, produced by the total dose D . The dose comprises contributions from the primary and secondary particles in the beam. Thus

$$\eta_L D = \sum_{i=1}^n \eta_{L,i} D_i = \sum_{i=1}^n \int \frac{\sigma_L(L)}{L} L \frac{d\phi_i}{dL} dL \quad (2)$$

where the summation is over all the different particle types in the beam. A similar equation can be written for $\eta_{PL} D$, and when these are substituted into equation (1), we obtain

$$S = \exp\{-\langle\sigma_L\rangle + \langle\sigma_{PL}\rangle\Phi\} \cdot \left[1 + \frac{T}{\epsilon} \langle\sigma_{PL}\rangle\Phi\right]^\epsilon \quad (3)$$

where we have substituted the expressions for the track-averaged values of the inactivation cross sections:

$$\langle\sigma_L\rangle = \frac{\sum_{i=1}^n \int \sigma_L(L) \frac{d\phi_i}{dL} dL}{\sum_{i=1}^n \int \frac{d\phi_i}{dL} dL} = \frac{\sum_{i=1}^n \int \sigma_L(L) \frac{d\phi_i}{dL} dL}{\Phi} \quad (4)$$

and

$$\langle\sigma_{PL}\rangle = \frac{\sum_{i=1}^n \int \sigma_{PL}(L) \frac{d\phi_i}{dL} dL}{\sum_{i=1}^n \int \frac{d\phi_i}{dL} dL} = \frac{\sum_{i=1}^n \int \sigma_{PL}(L) \frac{d\phi_i}{dL} dL}{\Phi} \quad (5)$$

In equation (3), Φ is the total fluence of particles and is the total absorbed dose, D , divided by the track-averaged LET, ϵ is the ratio of the correct (linear) repair rate to the (binary) misrepair rate, and T is a *repair factor*, $1 - \exp(-\epsilon_{PL} t_r)$, where t_r is the time available for repair. In this case, we assume that the time available for repair is long compared to the reciprocal of ϵ_{PL} , so that $T \approx 1$.

The cross sections for lethal and potentially lethal lesion formation are, respectively:

$$\sigma_L = \sigma_0 \{1 - [\exp(-k_0 \zeta)(1 + k_0 \zeta)]^m\} \quad (6)$$

and

$$\sigma_{PL} = F_{PL} \sigma_0 m k_0 \zeta \cdot \exp(-k_0 \zeta) \quad (7)$$

Here ζ is the ratio z^{*2}/β^2 where z^* is the effective charge of the particle and β is the velocity of the particle relative to that of light. Curtis, 1986, should be consulted for a discussion of how the functional form of these cross sections was developed.

There are five parameters in this model: ϵ , σ_0 , k_0 , F_{PL} , and m . ϵ has been defined above, σ_0 defines the effective cross sectional area within which the radiosensitive target(s) for lethal lesions reside, k_0 is a scaling factor that always multiplies z^2/β^2 , F_{PL} denotes the fraction that the potentially lethal cross section is of the lethal lesion cross section, and m is the mean number of times a particle track traverses the target(s).

Results

In Fig. 3 we show the product of the lethal lesion cross section, σ_L , times the LET spectrum, $d\phi/dL$, as a function of LET for each particle species in the beam at the distal peak position. This product is the integrand in the numerator of equation (4). The neon contribution is noted ($Z=10$), but the contributions of the secondary particles are not individually identified for reasons of clarity. We note the dominance of the neon contribution to lethal (i.e., irreparable) lesion formation. Fig. 4 shows the same product for the potentially lethal lesions, which are the repairable lesions in this model; they are the ones which interact (i.e., undergo binary misrepair) to produce the shoulder on the survival curve. The product is of the potentially lethal lesion cross section and the LET spectrum; it is the integrand in the numerator of equation (5). Here we note a larger contribution by the secondary particles, but the neon ions still dominate.

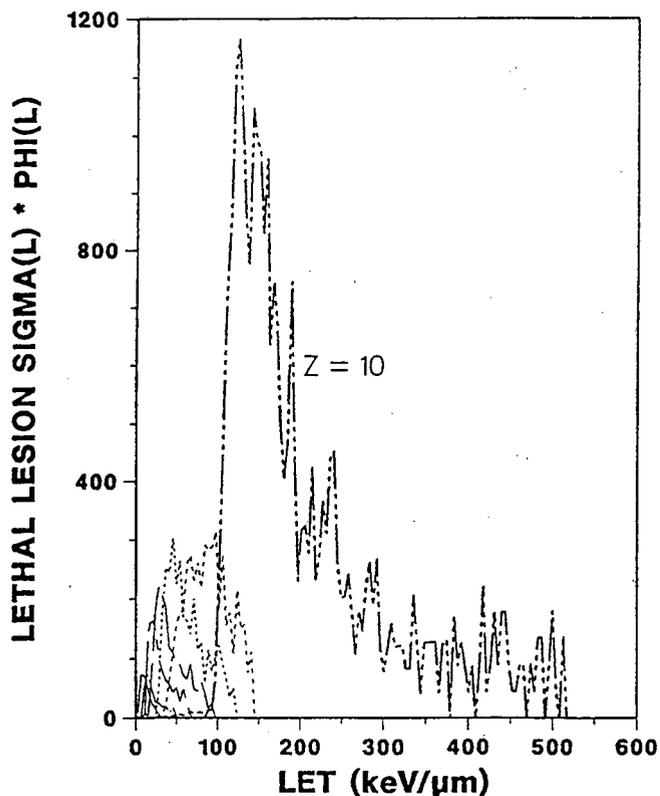


Fig. 3. The integrands in eq. (4) consisting of the product of the lethal lesion cross section and the LET spectrum for neon ($Z=10$) and the secondary particles at the distal position of the 12-cm spread peak. The secondary nuclear fragments are plotted individually but not identified for reasons of clarity.

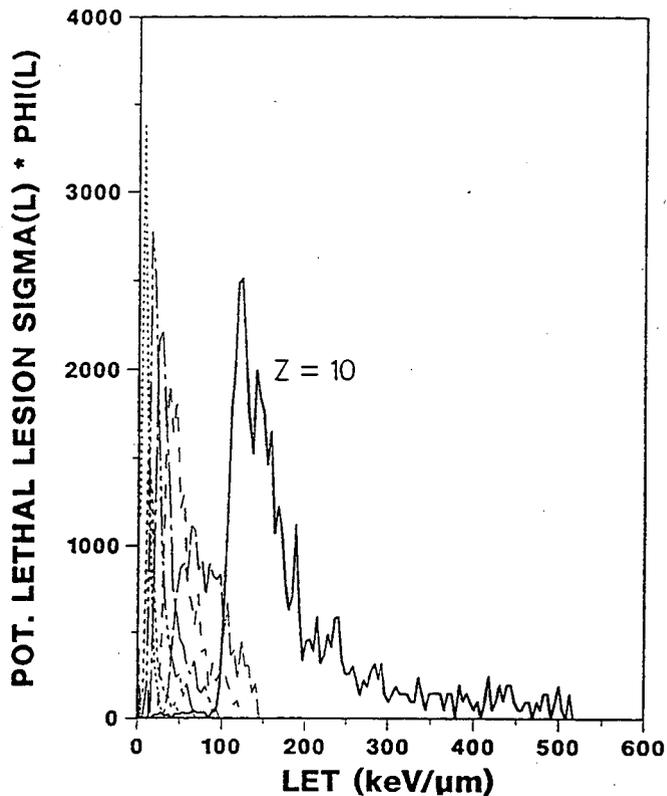


Fig. 4. The integrands in eq. (5) consisting of the product of the potentially lethal lesion cross section and the LET spectrum for neon ($Z=10$) and the secondary particles at the distal position of the 12-cm spread peak. The secondary nuclear fragments are plotted individually but not identified for reasons of clarity.

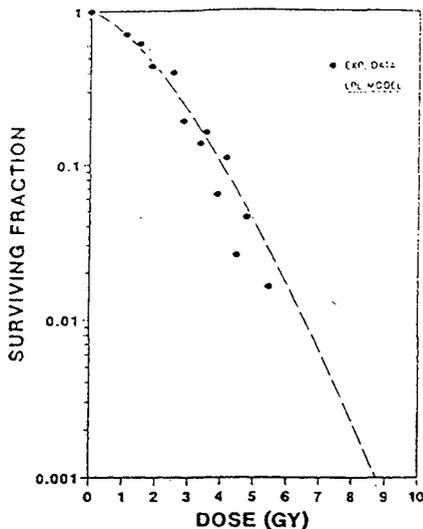


Fig. 5. Cell survival in the proximal position. The dashed line is the LPL model calculation and the filled circles are the experimental points obtained with human T-1 cells.

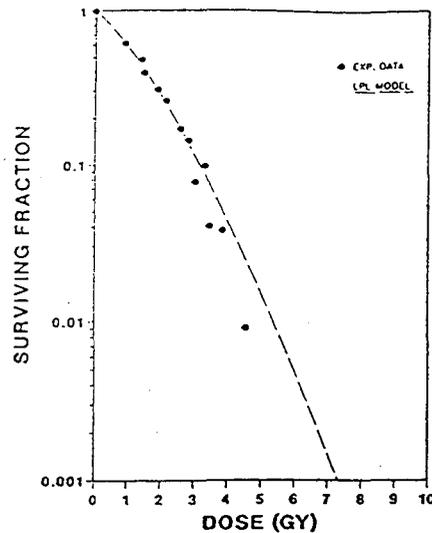


Fig. 6. Cell survival in the distal position. The dashed line is the LPL model calculation and the filled circles are the experimental points obtained with human T-1 cells.

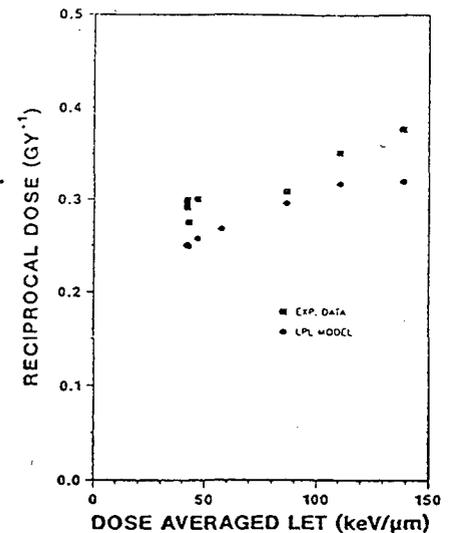


Fig. 7. The reciprocal of the dose to produce 10% survival is plotted for both calculated and experimental results as a function of dose-averaged LET for various beams, energies and spread-peaks.

The resulting calculated survival curves at both the proximal and distal positions of the spread-peak are given in Figs. 5 and 6, respectively, along with the experimental cell-survival results using human T-1 cells. The parameters in the model were chosen from an earlier analysis of T-1 cell survival after alpha particle irradiation (Barendsen *et al.*, 1966). The values are $\epsilon=9$, $\sigma_0=45 \mu\text{m}^2$, $k_0=1/4000$, $F_{PL}=0.1$ and $m=12$. We note a good agreement between the calculated curves and the experimental results up to 4 Gy. At higher doses the experimental points tend to be lower than the model calculations.

Finally, the reciprocal of the dose to produce 10% cell-survival (which is proportional to $\text{RBE}_{0.1}$) is plotted as a function of the dose-averaged LET in Fig. 7. Here values are shown from various different beams of ions with different initial energies and at different places throughout spread-peak beams of different widths. Results from the model calculations are compared with experimental results. A striking result is that at least for radiations in the LET range covered by these experiments, dose-averaged LET appears to be a fairly good indicator of biological effect. This would not be expected if differences in track structure of ions at the same LET played a significant role in modifying the biological effect. Thus for therapeutic application, dose-averaged LET might be considered as a candidate physical descriptor for determining cell-killing efficacy.

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