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Abstract

Unanticipated late effects in neutron and heavy ion therapy, not attributable to overdose, imply a qualitative difference between low and high LET therapy. We identify that difference as 'ion kill', associated with the spectrum of z/β in the radiation field, whose measurement we label 'ion-kill dosimetry'.

KEYWORDS: Ion-kill, biological dose, late effects, heavy ion therapy.

1. Late Effects in Heavy Ion Therapy

Neutron therapy in the UK has been accompanied by unanticipated late effects, associated with loss of repair, leading to the closing of all three installations [1]. Such effects have also been observed at Berkeley with silicon and neon [2]. In discussing experience with He and Ne, Castro [3] mentioned that tumor doses were expressed in physical Gray and Gray equivalent. He stated that this was of some value with protons or helium but was not as valid or useful for heavier ions such as neon. Further, fractionation did not protect against late effects for neon as is the case for low-LET radiation. In all cases treatment planning was based on 'biological dose', the product of RBE and physical dose. Since extensive and accurate measurements of RBE preceded treatment, the failure cannot be attributed to overdose. We must conclude that biological dose is an inadequate concept for high LET therapy, though adequate for protons and helions. A quantitative dosimetry which recognizes the qualitative difference between photons and heavy ions is required. We propose that such a dosimetry can be based on track theory.

2. A Precis of Track Theory

To explain the shapes of survival curves observed with many different cell lines and different particle beams we invoked a theory of dual radiation action, the two modes being called ion-kill and gamma-kill. Ion-kill is the effect produced by single energetic heavy ions traversing a cell nucleus, while gamma-kill is the effect produced by delta rays from adjacent ions on cells at most sub-lethally inactivated by single ion traversals. In both cases the effects are produced by delta rays, but the high concentration of low energy delta rays close to an ion's path is a much more severe effect than that produced by the dispersed delta rays from different ions in the gamma-kill mode.

Gamma-kill physically resembles the inactivation by the Compton- and photo-electrons from photon irradiation. Ion–kill is responsible for all high-LET effects: elevated RBE, reduced OER, loss of repair, insensitivity to cell cycle differences.

In the theory the probability for ion-kill is used as an approximation for the fraction of the dose consumed in the ion-kill mode, with the residue called the gamma-kill dose. Ion-kill effects are calculated from the ion-kill cross section and the particle fluence, while gamma-kill effects are calculated from the same multi-target formula used for calculating the survival curve for gamma-rays. Thus the gamma-kill dose is fully equivalent to an equal photon dose, as confirmed by our calculations of the effects of radiation fields in which neutrons were admixed with photons [4].

The theory requires the evaluation of four radiosensitivity parameters from a collection of survival curves after exposure to particle beams of different composition and LET. Once evaluated these parameters are used to calculate the response of arbitrary radiation fields whose particle-energy spectrum is known from calculation, for this measurement is presently impossible. But the theory has shown that an arbitrary radiation field can be reduced to the total ion-kill probability, and the total gamma-kill dose. The ion-kill probability can be calculated from the distribution in the spectrum of z/β in the radiation field and the radiosensitivity parameters. From the theory a measurement of total dose, and a measurement of the ion-kill probability can yield calculations of cell survival, RBE and OER for those cells where in vitro measurements have yielded radiosensitivity parameters [5]. We anticipate that clinical experience will identify the choice of radiosensitivity parameters appropriate to different tissues and the levels of ion-kill and dose correlated with unacceptable complications in high LET therapy.

3. Calculations of Ion-Kill, RBE, and cell survival in a 2 cm spread Bragg Peak

To investigate the relation of ion-kill to these problems we have calculated profiles of cell survival, physical dose, RBE, and probability for survival in the ion-kill mode for beams of H, He, C, and Ne, in a 2 cm spread Bragg peak, for which there is 30% iso-survival [6]. This paper should be consulted for further background, formulas and illustrations for which there is no space here. The regular decrease in ion-kill from neon through carbon and helium to protons is consistent with clinical observation of late effects, and has led us to identify ion-kill as the source of this problem. Although we have not yet calculated the distribution of ion-kill probability as a function of depth in neutron irradiated tissue, some of our earlier work [7] yielded a calculation of the ion- kill probability for neutrons of known initial energy for which the fragment particle-energy distribution had been calculated from experimental cross sections (Caswell and Coyne and Dennis, pvt. communication). There the ion kill probability increased regularly from about 0.24 for 14 MeV neutrons to 0.65 for 0.5 MeV neutrons, for hamster cells, with small variation for other cell lines. The neutron energy spectrum for the MRC installation at Hammersmith hospital yielded a value of 0.2, while that from pion stars was 0.15.

4. Ion Kill Dosimetry

Now, as to ion kill dosimetry. Clearly, we require discriminating detectors, which respond preferentially to single energetic heavy ions compared to single electrons or protons, as is the case for biological cells. Studies from track theory have identified a number of such discriminating detectors in physics and chemistry. Our preferred initial selection is the class of solid state track etch detectors where a heavy ion transit through the detector creates a latent damage trail which is exposed by chemical etching. In their application to the measurement of the particle spectrum of cosmic rays it has been useful to correlate 'etching rate', the size of etch pits after specified etching times, to z/β [8]. Different detectors span a range of this quantity from 10 to 250 for relativistic cosmic rays. They can be expected to be useful for the evaluation of the biological effect of single heavy ions in space. We will investigate their utility for the spectrum of energetic heavy ions in cancer therapy. Knowledge of the spectrum of z/β in tissue may be converted to the spectrum of ion kill probability by use of track theory. We anticipate that this new information will aid radiation oncologists in their treatment planning, to avoid late effects while yet taking advantage of the beneficial effects of high LET radiation

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