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A COMPARISON OF THE DOSE · RBE AND THE BIOLOGICAL DOSIMETRY APPROACHES FOR TREATMENT PLANNING IN BNCT

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Treatment planning for clinical trials with boron neutron capture therapy (BNCT) is complicated substantially by the fact that the radiation field generated by the activating external neutron beam is composed of several different types of radiation, i.e., fast neutrons, recoil protons from elastic collisions with hydrogen, gamma rays from the reactor and from neutron capture by body hydrogen, protons from nitrogen capture, and the products of the NCT interaction. Furthermore, the relative contribution of each type of radiation varies with depth in tissue. Because each of these radiations has its own RBE, and the RBE of the fast neutron component will not be constant as the neutron spectrum changes with depth, the problem of predicting the severity of the biological effect, in depth, becomes complex indeed.

In order to attack this problem, Monte Carlo calculations of dose, checked against benchmark measurements, are employed. Two approaches are then used to assess the severity of the effect. In the first, the effective dose (D_{EF}) is determined by summing the products of ($D \cdot RBE$) for each radiation. The other approach, "biological dosimetry", involves placing cells at the location for which the D_{EF} was calculated. Using a dose-response curve from a low-LET radiation, e.g. ^{137}Cs gamma rays ($D_{\gamma, \text{Cs}}$), the "photon equivalent dose" (PED, or D_p) can be determined. If the RBE values used are correct, the D_{EF} and the D_p should be essentially identical.

In our preliminary experiments, the agreement was not satisfactory. The object of this paper is to describe these initial efforts in some detail, and then outline our plans for attempting to reconcile the differences. Because we regard Monte Carlo as an essential part of treatment planning, it is imperative that this complex problem be resolved.

The first step was to establish an apparent RBE (RBE_a) for fast neutrons in the epithermal beam of the Brookhaven Medical Research Reactor (BMRR). Cells were irradiated, in air, at the epithermal beam of the BMRR in a configuration and geometry that yielded ~4% thermal neutrons. Thus, the major dose components were fast neutrons, gamma rays and protons from the n,p reaction with nitrogen. An RBE of 1 was used for gamma, and an RBE_a of 2 for the protons, a value that has been estimated (1), and measured (2)¹. For the BMRR experiments, survival was first plotted as a

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¹The term RBE_a is applied here since the measurements in (2) were carried out in a mixed-field.

Table I. Physical doses for BMRR phantom experiment (all doses given in Gy)

Position	D _{nk}	D _{t,api}	D _γ	D _{boron}	D _{tot}
1	0.522	0.720	2.349	----	3.591
% D _{tot}	14.5	20.0	65.4	----	~100
2	0.621	0.414	3.114	----	4.149
% D _{tot}	14.9	9.9	75.0	----	~100
3	0.450	0.243	2.880	----	3.573
% D _{tot}	12.6	6.8	80.6	----	~100
4	0.270	0.135	2.115	----	2.520
% D _{tot}	10.7	5.4	83.9	----	~100
1*	0.174	0.264	0.783	2.178	3.399
% D _{tot}	5.1	7.8	23.0	64.1	~100
2*	0.207	0.138	1.038	2.496	3.879
% D _{tot}	5.3	3.6	26.8	64.3	~100
3*	0.150	0.081	0.960	1.809	3.000
% D _{tot}	5.0	2.7	32.0	60.3	~100
4*	0.090	0.045	0.705	1.074	1.914
% D _{tot}	4.7	2.4	36.8	56.1	~100

* with 30 μg/g enriched boric acid

function of MW minutes. This was subsequently converted to dose (D) by means of Monte Carlo calculations, which yielded a conversion factor of Gy/MW min (3). Cell survival curves for the BMRR and ¹³⁷ Cs gamma rays are shown in Figs. 1 and 2. Note the absence of effect from boric acid with the ¹³⁷ Cs gamma rays. Irradiation techniques and cell culture assay methods are detailed elsewhere (4,5). The 10% level of survival was selected for the determination of both D_{EF} and D_p.

Assuming that the RBE_n of 2 for the 0.6 MeV protons from nitrogen capture is correct, the RBE_n for the fast neutrons was determined by means of the following equation:

$$D_{EF} = D_{prot} \cdot RBE_n + D_{\gamma} \cdot RBE + D_{neut} \cdot RBE_n \quad (1)$$

Substituting the D_p for the D_{EF}, and using the RBE's above, the RBE_n for fast neutrons was calculated to be 3.6.

We then placed cells at depth (1.4, 3.6, 5.8, and 8 cm) in a lucite phantom, and the RBE for neutrons was again determined. The arrows in Fig. 3 show the sequential positions of the cell holders for these irradiations (position 1 is nearest the beam). Physical doses are given in Table I. The RBE_n for fast neutrons at position 1, calculated by substituting D_p for the D_{EF} in equation 1, was found to be 4.8. Thus, in order to make D_{EF} equal to D_p, it was necessary to adjust the RBE for fast neutrons upward, from 3.6 to 4.8.

To determine an RBE_n for the boron reaction products, the following equation was used:

$$RBE_{n, boron} = D_p / D_{boron} \quad (2)$$

When 30 μg¹⁰B/g boric acid was used, the RBE_n was calculated to be 3.6, closely approximating that reported earlier (6). As shown in Table II, the D_{EF} is equal to the D_B in the first two cell

Table II. RBE_n for neutron and boron doses

Position	Physical dose (Gy) BMRR	Per cent survival	Absorbed dose (Gy) ¹³⁷ Cs	RBE _n neutrons (fast)	RBE _n Boron-10 (30μg/g)
1	3.6	9.6	7.2	4.8	---
2	4.1	17.6	6.2	4.8	---
3	3.6	12.3	6.7	11.9 (?)	---
4	2.5	29.8	4.2	11.4 (?)	---
1*	3.4	2.4	10.3	4.8	3.6
2*	3.9	2.2	10.2	4.8	3.6
3*	3.6	2.6	10.3	31.0 (?)	3.6
4*	1.9	13.5	6.5	38.9 (?)	3.6

RBE nitrogen, assumed 2

RBE gamma, assumed 1

*with 30 μg¹⁰B/g boric acid

positions only (1,1*,2,2*). For positions 3 and 4, major adjustments in the apparent RBE's were required in order to make D_{EF} equal to D_p.

Several factors may be influencing the apparent effectiveness of the various radiations at depth in the phantom. The gamma dose, relative to the fast neutron dose, increases with depth (Table I). Also, the energy spectrum of the fast neutrons changes with depth, which should increase the RBE. The high and low LET radiations may act synergistically (7), and the RBE of 2, assumed for recoil protons, may not be correct. Because the absolute value for the dose of neutrons decreases rapidly with depth, the calculated neutron dose may be imprecise. The neutron dose in depth is low, so it may result in using a large number to adjust the dose.

Figure 3

It is evident that the use of Monte Carlo calculations and assumed RBE's did not provide an accurate assessment of the effective dose in our experiments designed to simulate patient treatment planning for BNCT. The difficulties attendant upon the approach include, a) the accuracy of the RBE values for all components are in question because they can not be determined separately, and b) additional mechanisms involved in the interactions may change the severity of effect (e.g. synergism).

It is our contention that a cell system which is highly reproducible with respect to its response to photon irradiation should be used as a bench mark measurement of the PED, and thus of the true D_{EF} for BNCT radiations. We intend to pursue these studies further by positioning cells at given regions of interest in a phantom that is tissue equivalent for neutrons. Their response will be evaluated with and without boron, under conditions of homogeneous and heterogeneous intracellular boron distribution. It is anticipated that the difficulties outlined above can be resolved so that the approach using calculations, measurements, RBE and D_{EF} can provide a realistic and precise prediction of the severity of biological effect at any pre-determined site.

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Dose Response Curve, Mixed Field Radiations (BMRR)

Dose Response Curve, ^{137}Cs Gamma Rays

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