XA0101248

Annex 6
RADIOBIOLOGY

The radiobiology of boron neutron capture therapy: Are "photon-equivalent" doses really photon-equivalent?

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Abstract. Boron neutron capture therapy (BNCT) produces a mixture of radiation dose components. The high-linear energy transfer (LET) particles are more damaging in tissue than equal doses of low-LET radiation. Each of the high-LET components can multiplied by an experimentally determined factor to adjust for the increased biological effectiveness and the resulting sum expressed in photon-equivalent units (Gy-Eq). BNCT doses in photon-equivalent units are based on a number of assumptions. It may be possible to test the validity of these assumptions and the accuracy of the calculated BNCT doses by 1) comparing the effects of BNCT in other animal or biological models where the effects of photon radiation are known, or 2) if there are endpoints reached in the BNCT dose escalation clinical trials that can be related to the known response to photons of the tissue in question. The calculated Gy-Eq BNCT doses delivered to dogs and to humans with BPA and the epithermal neutron beam of the Brookhaven Medical Research Reactor were compared to expected responses to photon irradiation. The data indicate that Gy-Eq doses in brain may be underestimated. Doses to skin are consistent with the expected response to photons. Gy-Eq doses to tumor are significantly overestimated. A model system of cells in culture irradiated at various depths in a lucite phantom using the epithermal beam is under development. Preliminary data indicate that this approach can be used to detect differences in the relative biological effectiveness of the beam. The rat 9L gliosarcoma cell survival data was converted to photon-equivalent doses using the same factors assumed in the clinical studies. The results superimposed on the survival curve derived from irradiation with Cs-137 photons indicating the potential utility of this model system.

1. BNCT DOSE COMPONENTS

In tissue, boron neutron capture therapy (BNCT) produces a mixture of components with differing linear energy transfer (LET) characteristics. Thermal neutron capture by ^{10}B, the $^{10}B(n,\alpha)^{7}Li$ reaction, releases high-LET alpha and lithium particles with a track length in tissue of approximately 10 μm. The interaction of the neutron beam with the nuclei of other elements in tissue will deliver an unavoidable, non-specific background dose, from a mixture of high- and low-LET radiation components, to both tumor and normal tissue. Thermal neutron capture by hydrogen releases a gamma ray through the $^{1}H(n,\gamma)^{2}H$ reaction. The capture of thermal neutrons by nitrogen in tissue, the $^{14}N(n,p)^{14}C$ reaction, releases a high-LET proton with an energy of 590 keV. Contaminating fast neutrons (those with kinetic energies >10 keV) in the epithermal neutron beam produce high-LET recoil protons with similar average energy through collisions with hydrogen nuclei ($^{1}H(n,n')p$ reaction) in tissue. These dose components each vary differently as a function of depth, and could vary considerably between different epithermal neutron beams.

2. WHY EXPRESS BNCT DOSES IN PHOTON-EQUIVALENT UNITS?

Due to the high density of ionizations produced along the particle track, high-LET radiation generates more damage in biological systems than an equal physical dose (in Gy) of low-LET radiation Dose components with different LET characteristics will have different

degrees of biological effectiveness with regard to tumor and to the various normal tissues within the treatment volume, such as the CNS and the skin. To express the total BNCT dose to a given tissue in a common, photon-equivalent unit, each of the high-LET dose components (physical dose in Gy) is multiplied by an experimentally determined biological effectiveness factor. The total, photon-equivalent BNCT dose can then be expressed as the sum of the biological effectiveness-corrected physical absorbed dose components, using a unit defined as the Gray-Equivalent (Gy-Eq). The biological effectiveness factors will be different for different tissues such as tumor, brain or skin. These biological effectiveness factors will also differ among different boron compounds.

Why use photon-equivalent dose units in BNCT? The use of Gy-Eq doses in a dose escalating BNCT clinical protocol allows a consistency in the dose estimation, even if the relative contributions of each different dose component may be changing as the total dose is escalated or as the treatment parameters are changed (e.g., progression from 1-field, to 2-fields, to 3-fields). Perhaps more importantly, the use of Gy-Eq units in BNCT dose estimation allows a comparison of doses delivered at different institutions. The currently available clinical epithermal beams being used for BNCT differ considerably in the relative proportions of the various dose components. Is 10 Gy total physical dose the same at two different treatment centers? Not necessarily. Figure 1 shows an example of two hypothetical epithermal neutron beams. Both beams are used to deliver a reference dose (to 1 cm^3) of 10 Gy to normal brain. Beam 2 has a different mixture of dose components compared to Beam 1; 4 times more fast neutrons, 50% of the thermal fluence, and slightly higher (16%) gamma component. The Gy-Eq doses shown in Figure 1 for both of these hypothetical beams are calculated using the biological effectiveness factors in current use in the Brookhaven clinical trial [1,2]. It is clear that even though the physical doses are the same, the Gy-Eq doses are considerably different: 15 Gy-Eq for Beam 1 versus 20 Gy-Eq for Beam 2.

3. BIOLOGICAL EFFECTIVENESS FACTORS

The dependence of the biological effect on variations in the microdistribution of different boron compounds, and of the same boron compound in different tissues, makes the term relative biological effectiveness (RBE), as generally understood, inadequate for fully defining the biological effectiveness of the $^{10}B(n, \alpha)^7Li$ reaction. RBE is usually defined as the ratio of doses of a reference radiation (generally X rays) to a test radiation that will produce the same biological endpoint in a given system. Measured in this way, the RBE is solely a function of the quality (LET) of the test radiation. In BNCT radiobiology, measured biological effectiveness factors for the component of the dose from the $^{10}B(n, \alpha)^7Li$ reaction have instead been termed compound factor [3] or compound biological effectiveness (CBE) factor (cf. [4]).

The approach to experimental determination of these biological effectiveness factors has been recently reviewed [5]. The general approach is as follows: 1) for each tissue, define a quantifiable endpoint or response to irradiation; 2) determine the dose response to a photon reference radiation; 3) determine the dose response to the neutron beam only; and 4) determine the dose response to the neutron beam in the presence of the boron compound. Once these dose response relationships have been determined, it is possible to estimate a

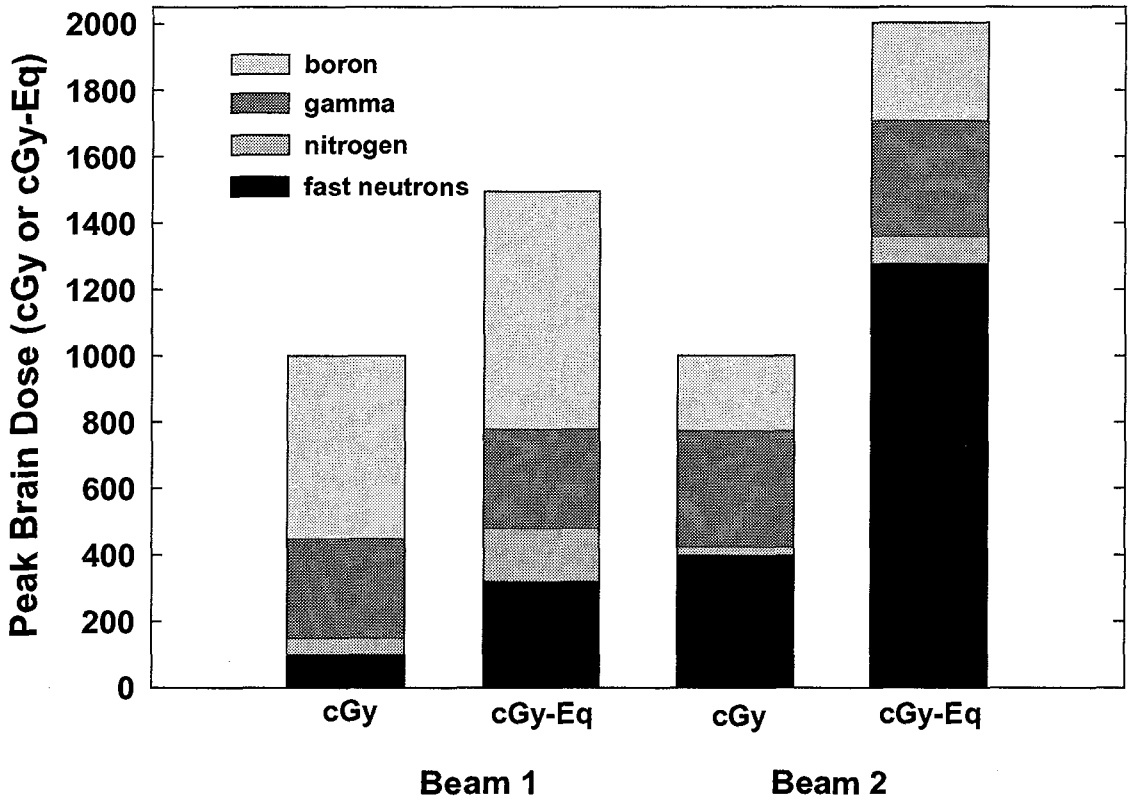

FIG. 1. Comparison of two hypothetical beams with equal peak physical dose in brain, but different photon-equivalent doses.

number of useful quantities: 1) the RBE of the beam alone, 2) the RBE of the high-LET components of the beam (nitrogen capture dose plus the fast neutron recoil proton dose), 3) the biological effectiveness factor for the particular boron compound.

In the following discussion, the "proton dose" is used to refer to the high-LET components of the neutron beam: the 590 keV protons released from thermal neutron capture reactions in nitrogen and the recoil protons resulting from the collision of fast neutrons in the beam with hydrogen atoms in tissue. Because their energies tend to be in the same range, the uniformly distributed effects of the nitrogen capture proton and the fast neutron recoil proton are most conveniently measured as a combined "proton dose".

A measure of the RBE for the neutron beam can be obtained, in the absence of boron, by comparing the neutron beam dose with the X ray dose sufficient to produce an isoeffect in a given biological system. The result can be expressed as in [Eq.1], where ED_{50} is the physical absorbed dose which results in a 50% incidence of the biological endpoint under evaluation. This assumes that the beam dose comprises gamma plus a combined "proton dose" as described above and that the RBE of the gamma component is 1. The beam RBE is the ratio of the x ray dose and the beam dose at the ED_{50} effect level [Eq. 2].

$$\text{["proton" dose]} + \text{[gamma dose]} = \text{X ray } ED_{50} \text{ dose} \qquad \text{[Eq. 1]}$$

$$\text{beam RBE} = \text{[X ray } ED_{50} \text{ dose]/\{ ["proton" dose] + [gamma dose] \}} \qquad \text{[Eq. 2]}$$

An estimate of the RBE for the high-LET components of the beam can be obtained in the absence of boron from the same data by expressing the result as in [Eq. 3] and solving for the "proton" RBE as shown in [Eq. 4].

["proton" dose]["proton" RBE] + [gamma dose] = X ray ED_{50} dose [Eq. 3]

"proton" RBE = [X ray ED_{50} dose — gamma dose]/ ["proton" dose] [Eq. 4]

Experimentally, the CBE factor can be evaluated by first comparing the effect of the beam alone to the effect of a reference radiation to obtain an estimate of the beam RBE or of the high-LET components of the beam as described above. Thermal neutron irradiation, with boron compound present, to a total dose producing the same ED_{50} endpoint is represented by [Eq. 5]. Solving [Eq. 5] for the CBE factor produces [Eq. 6].

X ray ED_{50} dose = [Beam dose][Beam RBE] + $^{10}B(n,\alpha)^{7}Li$ dose][CBE factor] [Eq.5]

CBE factor = { [X ray ED_{50} dose] — [Beam dose][Beam RBE] }/ [$^{10}B(n,\alpha)^{7}Li$ dose] [Eq.6]

The short range of the particles released from the $^{10}B(n,\alpha)^{7}Li$ reaction make the biodistribution of the particular boron compound of critical importance in experiments designed to measure CBE factors. The various experimental conditions under which CBE factors can be measured means that a number of variables will contribute to the overall biological effect. The mode of compound administration, the boron distribution pattern within the cell and within the tissue, the dose per fraction and even the size of the nucleus in the target cell population all may influence the experimental determination of a CBE factor. It is critical that experimental determinations of CBE factors be done under conditions that approximate the clinical situation as closely as possible. For example, studies with BPA in the rat spinal cord have shown that the CBE factor is dependent on blood:spinal cord ratio [6]. For BPA, CBE factor values from 0.66 to 1.33 were obtained depending on experimental conditions.

4. VALIDATION OF PHOTON-EQUIVALENT DOSES

The calculation of Gy-Eq doses delivered to tumor and to normal tissues in BNCT requires estimates of three basic parameters: 1) the boron concentrations in tumor and normal tissues, 2) the CBE factors for that particular boron compound in tumor and in all normal tissues within the treatment field, and 3) the RBE of the high-LET components of the beam itself for tumor and for the normal tissues involved.

Validation of the calculated photon-equivalent doses currently being used in BNCT clinical trials can come from a) animal models, where the effects of Gy-Eq doses delivered during boron neutron capture irradiations can be compared to the known response of the tissue to photon irradiation; or b) from the clinical data, if there are endpoints reached in the BNCT dose escalation trials that can be related to the known response to photons of the tissue in question. The following sections on skin/mucosa, brain, and tumor attempt to bring together data from animal studies and/or the preliminary data from the Brookhaven BNCT clinical trial [1,2,7] to estimate the accuracy of the calculated Gy-Eq BNCT doses.

4.1. Skin/Mucosa

The BNCT program in Japan, in the course of treating human malignant melanoma using BPA and thermal neutrons, has produced important information on the effect of this treatment on human skin [8]. Based on boron measurements in blood and skin, these investigators estimated the boron concentration in the skin at the time of BNCT to be between 1.3 and 1.5 times the concurrent level in the blood. This is in agreement with the data from the Brookhaven clinical biodistribution data [7]. The threshold for moist desquamation in human skin after a single dose of photons was taken to be 18 Gy. By comparing the calculated doses to the skin and the observed incidence of moist desquamation, these authors were able to estimate the biological effectiveness factor for the combined effects of the nitrogen capture reaction and the boron neutron capture reaction as approximately 2.3 to 2.5.

In the Brookhaven BNCT trial, the calculated dose to the scalp is based on the measured boron concentration in the blood at the time of BNCT, assuming a blood/scalp boron concentration ratio of 1.5:1 [1,7,8]. Recent studies in rats have shown that the boron concentration in oral mucosa is twice the concurrent level in the blood [9]. Calculated BNCT doses to mucosa assume this value of two times the blood. For both skin and mucosa, an RBE for beam "protons" of 3.2 is assumed. For mucosa and for skin, a CBE factor of BPA of 2.5 is used [8]. This value is somewhat lower than the CBE factor value of 3.7 measured for BPA with moist desquamation of rat skin as the endpoint [10], which could be related to structural differences in the architecture of the vascular supply between the loose skin of rats and the fixed skin of humans. The CBE factor measured for BPA using ulceration of the undersurface of the rat tongue as a model for oral mucosa was approximately 5 [9].

In photon radiotherapy single-fraction doses of approximately 18 Gy produce moist desquamation, which is generally considered to indicate the tolerance limit in clinical radiotherapy [11]. Single-fraction doses substantially larger than 18 Gy result in critical damage to the vasculature in the underlying dermis resulting in dermal necrosis. Depending upon the photon energy, the maximum tolerance dose for human skin (dermal necrosis endpoint) following a single exposure is estimated to range from 22.5–30.0 Gy [12].

In the series of dog irradiations carried out using BPA-fructose and the epithermal neutron beam at the Brookhaven Medical Research Reactor, the calculated doses to the scalp ranged from 12–20 Gy-Eq. The skin response consisted of epilation, loss of pigmentation and a mild dry desquamation. The dog that received the highest dose developed small areas (1–2 mm) of moist desquamation. In the BNCT clinical trial at Brookhaven, the calculated scalp doses range from 10 to 19 Gy-Eq. The observed effects include only epilation and a mild erythema. In the Brookhaven BNCT clinical trial, there have not been enough documented incidences of side effects to estimate the accuracy of the calculated Gy-Eq doses to mucosa. At least for skin, the available data from dog and human BNCT irradiations indicate that the mild reactions observed to date following calculated BNCT doses, which have all been below 20 Gy-Eq, are consistent with the (lack of) response expected from photon irradiation.

4.2. Brain

The rat spinal cord model has been used to quantify the biological effectiveness of BNCT in the normal CNS [4,6,13]. The late radiation-induced effects seen in the spinal cord following a single fraction of BNCT are similar to those seen in the brain [14]. The sensitivities of the rat

brain and spinal cord to fractionated irradiation are also comparable [15]. The end point of limb paralysis (myeloparesis) for the evaluation of late radiation-induced spinal cord damage is clearly defined while histopathologic and histomorphometric endoints used to assess damage to the brain can be difficult to quantify.

Estimates of the tolerance of the normal brain to fractionated photon radiotherapy were converted to single-fraction equivalent doses using the linear quadratic formalism. For photon radiation, the threshold for necrosis is estimated to be approximately 13.8 Gy. Emami et al. estimated the risk of necrosis for irradiation of various brain volumes [16]. The calculated single-fraction dose producing a 5% risk of necrosis for irradiation of 1/3 of the brain volume is $\approx$ 14.5 Gy, and for irradiation of the whole volume, $\approx$ 13.2 Gy. The threshold for somnolence after whole brain radiation is estimated at approximately 7.3 Gy.

The photon-equivalent dose (Gy-Eq) to the normal brain is estimated from the measured boron concentration in the blood at the time of BNCT using a CBE factor for BPA of 1.3 [4], and an RBE of 3.2 for the beam "protons" [1]. The brains of 12 normal dogs were irradiated in the Brookhaven Medical Research Reactor epithermal neutron beam following i.v. infusion of 950 mg BPA/kg as the fructose complex. The maximum dose (delivered to 1 cm^3 of brain at the depth of maximum thermal neutron fluence) ranged from 7.8 Gy (11.8 Gy-Eq) to 11.8 Gy (17.5 Gy-Eq). The average dose delivered to the entire brain ranged from 5.8 Gy (8.5 Gy-Eq) to 8.5 Gy (12.2 Gy-Eq). All dogs were monitored by MRI for brain changes. Six dogs were sacrificed at varying time intervals due to onset of neurological complications. The remaining six dogs were sacrificed for histological analysis at 3 years post-BNCT, having shown little or no MRI changes and no neurological problems. In general, average whole brain doses up to 6.8 Gy (9.8 Gy-Eq) or peak doses up to 9.7 Gy (14.3 Gy-Eq) were well tolerated. Higher doses produced lethal brain necrosis.

Some BNCT patients that received whole-brain doses above 6 Gy-Eq have developed sub-acute side effects (somnolence). The follow-up period is not long enough on this group of patients to draw any conclusions about the accuracy of the calculated Gy-Eq doses. Further analysis, with more clinical response data, is required.

4.3. Tumor

For BPA, a method for the estimation of the boron concentration in tumor based on measured blood boron concentrations has been reported [17]. A morphometric index of the density of viable-appearing tumor cells in histologic sections obtained from samples adjacent to, and macroscopically similar to, the tumor samples used for boron analysis correlated linearly with the boron concentrations. From that correlation it is estimated that ^{10}B concentrations in glioblastoma tumor cells were 3.5–4 times greater than concurrent blood ^{10}B concentrations. The tumor/blood ^{10}B concentration ratio derived from this analysis provides a rationale for estimating the fraction of the radiation dose to viable tumor cells resulting from the boron neutron capture reaction. This method is based on measured boron concentrations in the blood at the time of BNCT without the need for analysis of tumor samples from individual patients. For BPA, a CBE factor value of 3.8 (range 3.6–4.0 for survival fractions of 10%, 1% and 0.1%, respectively) was derived in the 9L rat gliosarcoma model using an *in vivo/in vitro* clonogenic assay where intracranial tumors were irradiated *in situ*, surgically removed immediately after irradiation, and plated for colony-forming assay [18]. In summary, Gy-Eq BNCT doses to tumor use the following assumptions: 1) the boron concentration is 3.5 times higher than the concurrent level in the blood; 2) the CBE factor for BPA is 3.8; 3) the RBE for

beam "protons" is 3.2; 4) all tumor cells, including infiltrating cells, take up the same amount of boron; and 5) post-surgical tumor behaves like primary tumor.

Estimates of the magnitude of the dose required to control glioblastoma can be obtained from the photon or fast neutron literature. Stereotactic radiosurgery delivering a 15–35 Gy (20 Gy mean) boost to the tumor after 54–60 Gy of conventional fractionated photon therapy has proved to be locally effective in tumor control in the central portion of the treatment volume [19]. This treatment is roughly equivalent to a 30 Gy single-fraction treatment. Laramore has used the fast neutron experience to estimate that a single-fraction glioblastoma control dose should be in the range of 29–39 Gy-Eq [20].

The minimum tumor doses (deepest part of the contrast-enhancing tumor volume) calculated for the Brookhaven BNCT patients are all over 18 Gy-Eq, with a significant proportion over 30 Gy-Eq. Tumor recurrence has been local in the majority of cases, although extensive tumor necrosis has been documented in histological sections from some patients. Clearly, the Gy-Eq tumor doses are overestimates, or at least not all tumor cells are receiving the estimated doses. There are a number of assumptions behind the estimation of Gy-Eq doses to the tumor involving the delivery of boron to the tumor. Experiments are underway to address each of these assumptions more rigorously.

4.4. Radiobiological Dosimetry

Experimental determination of the RBE factors for the BNCT dose components has, for the most part, been carried out in thermal neutron beam experiments, either in vitro, or in small animals [5]. The exception is the dog work by Gavin [21] using the epithermal neutron beams at the High Flux Reactor, Petten, The Netherlands, and at the Brookhaven Medical Research Reactor. A direct measure of epithermal beam RBE in small animals is difficult due to the high whole body exposure. Build-up material would be required to thermalize the incident neutron beam.

A model system has been developed consisting of cells in culture placed at increasing depths in a lucite phantom in an effort to provide a direct measurement of the RBE of the epithermal neutron beam at the BMRR. Preliminary studies have shown that the technique of using cell survival at depth in a phantom in the epithermal beam can detect differences in beam RBE as a function of depth [22]. A method for direct measurement of the RBE of epithermal neutron beams could be of possible use in a number of applications such as: comparison of the beam RBE from different reactors or accelerator sources; investigation of the influence of dose per fraction on the beam RBE; investigation of whether beam RBE changes as a function of depth. This system may also allow vealidation of Gy-Eq doses. As an example, Figure 2 shows the survival fraction of rat 9L gliosarcoma cells as a function of increasing exposure time in the BMRR epithermal neutron beam. Cell vials were irradiated at depths of 1.0, 2.0, 3.5 and 7.0 cm in the lucite cube phantom. The relative proportions of the various dose components vary as a function of depth and, in addition, vary differently for each depth. Also shown in Figure 2 are survival curves for cells irradiated at 3.5 and 7.0 cm depth in the presence of boric acid at a concentration of 10 μg ^{10}B/ml. The presence of the boron greatly increases the cell kill. Figure 3 shows the dose response of the 9L cells to irradiation with Cs-137 gamma photons. In Figure 3, all of the dose components for the data points in Figure 2 have been multiplied by the appropriate biological effectiveness factors in a preliminary attempt to determine whether this set of factors produces photon-equivalent doses. The CBE factor used for boric acid was 2.3 [23]. Most of the BNCT data points superimpose

on the Cs-137 curve, indicating that the set of RBE and CBE factors do, indeed, generate photon-equivalent doses in this model system. This approach could be of use in further characterization of the response of biological systems to variations in the BNCT treatment parameters.

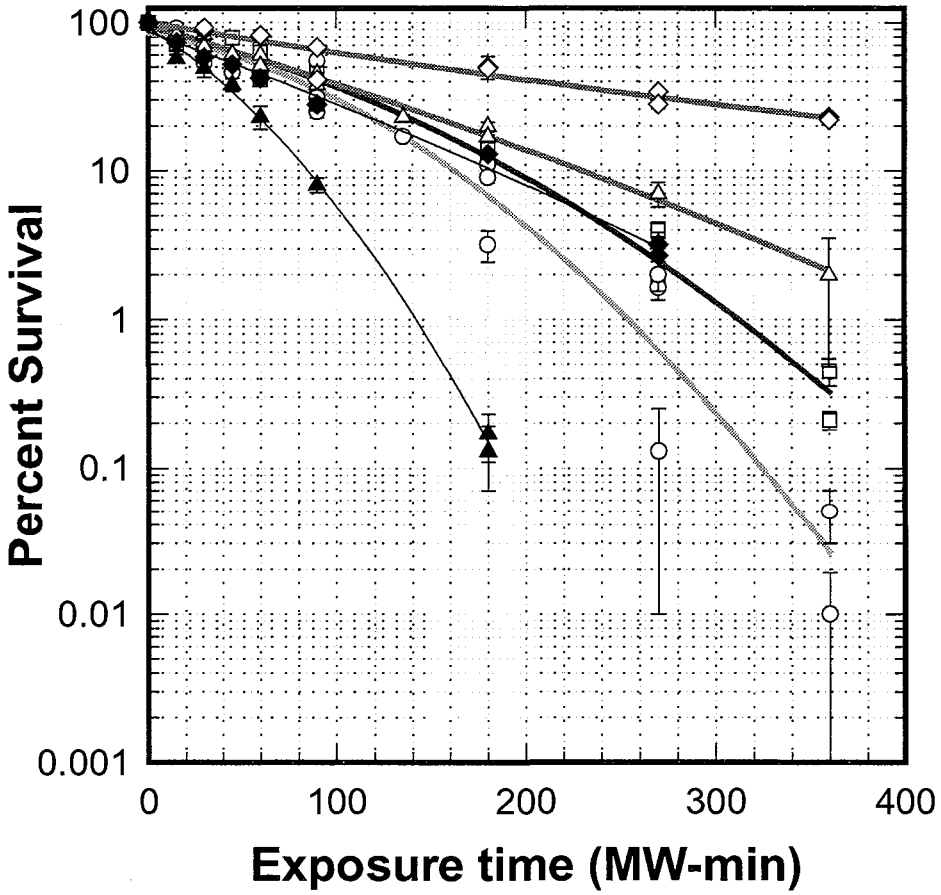

FIG. 2. Survival of rat 9L gliosarcoma cells as a function of exposure in the epithermal neutron beam. Cells were irradiated at various depths in a lucite phantom: open diamonds, 7.0 cm; open triangles, 3.5 cm; open squares, 2.0 cm; open circles, 1.0 cm; filled diamonds, 7.0 cm in the presence of boric acid (10 μg/ml ^{10}B); filled triangles, 3.5 cm in the presence of boric acid (10 μg/ml ^{10}B).

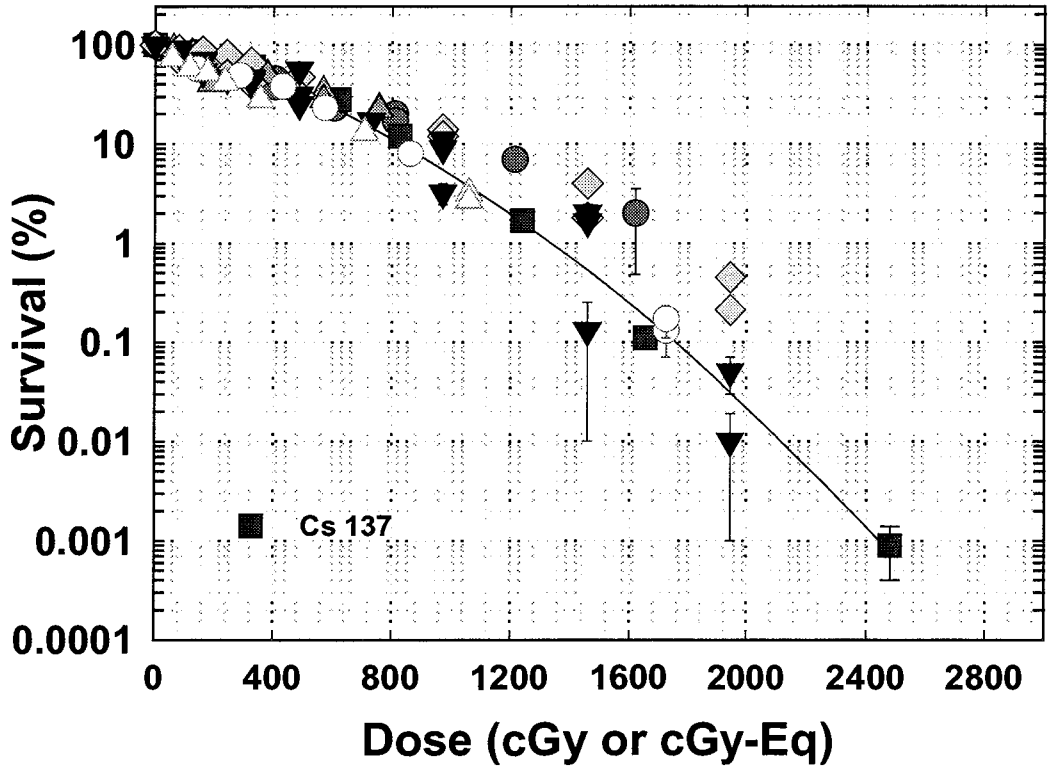

FIG. 3. Survival of rat 9L gliosarcoma cells as a function of exposure in the epithermal neutron beam. Cells were irradiated at various depths in a lucite phantom: triangle up, 7.0 cm; circle, 3.5 cm; diamond, 2.0 cm; triangle down, 1.0 cm; open triangle up, 7.0 cm in the presence of boric acid (10 μg/ml ^{10}B); open circle, 3.5 cm in the presence of boric acid (10 μg/ml ^{10}B). The data shown in Figure 2 was converted to Gy-Eq dose by multiplying the dose components by the following RBE or CBE factors: fast neutrons, 3.2, nitrogen capture, 3.2, boron capture (boric acid), 2.3, gamma, 1.0.

ACKNOWLEDGEMENTS

Gerard Morris and John Hopewell have been collaborators on all aspects of BNCT radiobiology. Supported by the Office of Biological and Environmental Research, U.S. Department of Energy, under contract number DE-AC02-98CH10886.

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