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# The influence of heavy water on boron requirements for neutron capture therapy

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Neutron penetration in tissue is a major limitation of thermal NCT, as such much work has centered upon the epithermal neutron beam in an effort to improve this situation. Further gains in neutron flux penetration, and thus therapeutic ratios, are possible if natural water is replaced with heavy water prior to therapy. Applying MCNP to a heterogeneous ellipsoidal skull/brain model, advantage depth and therapeutic depth parameters are studied as a function of heavy water replacement for a range of tumor to blood boron ratios. Both thermal (0.025 eV) and epithermal (2–7 keV) ideal neutron beams are analyzed. Using  $^{10}\text{B}$  ratios in the range of documented human uptake, the thermal advantage depth improved by approximately 0.7 cm for 20%  $\text{D}_2\text{O}$  replacement, however, the therapeutic depth increased by less than half this value. For the epithermal beam, both the advantage depth and the therapeutic depth increased by over 1 cm. Effects of heavy water replacement on  $^{10}\text{B}$  requirements to therapeutically treat the midline of the brain are also evaluated.

Key words: boron neutron capture therapy, advantage depth, therapeutic depth, MCNP, thermal, epithermal, heavy water

## I. INTRODUCTION

Boron neutron capture therapy (BNCT) involves the selective loading of tumor cells with compounds containing  $^{10}\text{B}$  and subsequent thermalized neutron irradiation. The  $^{10}\text{B}$  capture reaction generates short range, high linear energy transfer (LET) particles via the reaction  $^{10}\text{B} + n \rightarrow ^7\text{Li} + ^4\text{He}$ . 2.3 MeV is deposited within 12  $\mu\text{m}$  ( $\sim 1$  cell diameter), a fraction of which is in the cell nucleus. Double-strand breakage of DNA and subsequent reproductive cell death results. This technique has the potential to kill not only the main tumor body, but also any surrounding subclinical tumor cells while leaving healthy tissue undamaged. Glioblastoma multiforme (high grade astrocytoma) is characterized by a main tumor mass with accompanying fingerlets which infiltrate surrounding healthy tissue. These rapidly growing fingerlets render the theoretical cell specificity of BNCT an attractive possible treatment modality for this form of brain cancer. The history and current status of BNCT may be found in Brownell *et al.*,<sup>1</sup> and Allen *et al.*.<sup>2</sup>

The impact of deuterium replacement of hydrogen on neutron transport has been studied by Levine *et al.*,<sup>3</sup> Slatkin *et al.*,<sup>4</sup> and Kiszénick *et al.*<sup>5</sup> In biological applications, deuterium is best used as heavy water. Deuteration in mammals has been extensively studied<sup>6–10</sup> with conclusions that transient partial deuteration of body water is slightly to severely toxic to mice at the 20%–50% level, whilst long term deuteration is toxic at the 30% level. Blagojevic *et al.*<sup>11</sup> report heavy water concentrations in humans of up to 23% with no observed toxicity. Moderate deuteration (20%) of body water provides partial protection against whole body low LET radiation<sup>7,10,12,13</sup> but not high LET radiation from the  $^{10}\text{B}$  capture reaction.<sup>13</sup>

The BNCT mechanism requires two vital occurrences for success; (i) selective boron accumulation within the cancer-

ous tissues, and (ii) adequate thermalized neutron flux penetration. When limitations in the efficacy of BNCT with thermal neutrons became apparent in the clinical studies of Hatanaka,<sup>14</sup> heavy water replacement of light water was practiced in an endeavor to enhance the maximum therapeutic depth for thermal BNCT. Inclusion of heavy water in tissues significantly increases thermal neutron transmission with reduced capture  $\gamma$  ray absorbed dose rates,<sup>15</sup> and thus impacts on the  $^{10}\text{B}$  requirements for therapeutic treatment.

This paper evaluates treatment planning figures or merit as a function of heavy water replacement and tumor to blood boron ratios. Using MCNP,<sup>16</sup> Monte Carlo calculations were performed using an ellipsoidal heterogeneous skull/brain equivalent model.<sup>17,18</sup> Advantage depth and therapeutic depth parameters are studied as a function  $\text{D}_2\text{O}$  replacement ranging from 0 to 20% (molar). Ideal thermal (0.025 eV) and epithermal (2–7 keV) beams are examined with  $^{10}\text{B}$  tumor to blood ratios ranging from 1 to 10. Particular attention is paid to effective  $^{10}\text{B}$  uptake ratios in humans<sup>19</sup> of D,L,-p-boronophenylalanine (BPA) and boron sulfhydryl (BSH), and their requirements for therapeutic treatment of the midline of the brain.

Tumor to blood boron concentration ratios are commonly used in the BNCT field. The physical significance of blood boron concentration is that (i) depending on the compound, blood and healthy tissue boron levels may be different (this gives rise to the capillary dose reduction factor), and (ii) boron neutron capture in the bloodstream dominates the total dose to capillary endothelial cells. In BNCT of brain tumors, dose to capillary endothelial cells is expected to be the limiting factor.<sup>20</sup> Thus in this paper, dose to healthy tissue implies dose to healthy tissue capillaries. BPA and BSH are selected for their optimum tumor to blood boron ratios and thus their prospective effectiveness against glioblastoma

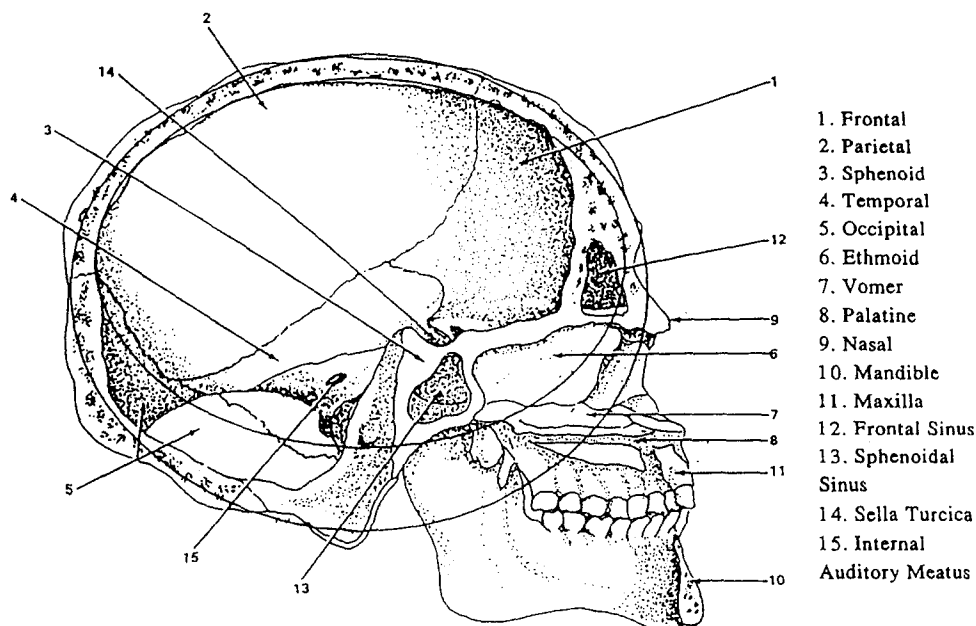


FIG. 1. The central sagittal plane of the head model superimposed on a human skull cross section. This figure shows how the head model simulates a human head.

multiforme. BPA passes the blood brain barrier with the net effect that blood boron concentration is approximately that of healthy tissue.<sup>20</sup> BSH however, does not pass the blood brain barrier but instead enters tumor cells via a breakdown of the barrier in the vicinity of the tumor.<sup>20</sup> This results in a blood boron level much greater than that in healthy brain tissue, which in turn leads to the capillary dose reduction factor for BSH.

## II. METHOD

### A. Model for Monte Carlo based dose computations

Using the MCNP transport code, the human brain and its surrounding structures were modelled using the geometry originally described by Snyder.<sup>17</sup> The skull/brain Monte Carlo model consists of two nonconcentric three-dimensional ellipsoids. Using a Cartesian coordinate system, the Z-axis is defined as the patient's superior-inferior axis, the X-axis is the lateral axis, and the Y-axis the anterior-posterior axis. Defining the volume of the brain, the inner ellipsoid is represented by the equation

$$(X/6)^2 + (Y/9)^2 + (Z/6.5)^2 - 1 = 0.$$

An outer ellipsoid, represented by

$$(X/6.8)^2 + (Y/9.8)^2 + [(Z+1)/8.3]^2 - 1 = 0$$

forms the exterior surface of the skull which surrounds the brain. X, Y, and Z are in cm.

Numerous measurements of CT scans of patients heads have indicated that the NPBE model is indeed closely representative in dimensions to the average human adult brain and skull.<sup>18</sup> This can be graphically seen in Fig. 1, courtesy Liu.<sup>21</sup> The brain volume enclosed by the inner ellipse is 1470 cm<sup>3</sup>, while the total bone volume is 847 cm<sup>3</sup>. These volumes are

typical of the average human brain and skull.<sup>17</sup> The elemental composition and densities of the 0% D<sub>2</sub>O model were that of average brain and skull as published in ICRU Report 46.<sup>22</sup> Tally volumes of 0.125 cm<sup>3</sup> (0.5 cm cubes) were constructed along the axes of the model. These were used as elementary volumes by the Monte Carlo simulation to record neutron and photon fluences resulting from incident neutrons. Measurement volumes were chosen on the basis of the results of Storr,<sup>23</sup> showing that using too large a tally volume (>1 cm<sup>3</sup>) results in erroneous advantage depth calculations.

15 cm diam neutron beams were applied from a lateral aspect onto the skull/brain model. These "idealized" beams consisted of a current of monoenergetic 0.025 eV neutrons for the thermal beam, and a uniform 2–7 keV spectrum representing the epithermal beam. Yanch *et al.*<sup>24,25</sup> have reported that a few keV is the most likely optimum neutron beam energy for use in BNCT. Ten cases were run, five each for both the thermal and epithermal beams, for molar heavy water replacements of 0, 5%, 10%, 15%, and 20%. Each simulation involved approximately 200 000 source neutrons, using 60 min cpu time on the ANSAMS Fujitsu VP2200 supercomputer with a final statistical error of approximately 5%. To include molecular effects upon thermal neutron scattering, the <sup>1</sup>H within the skull and brain materials was modeled as light water using the thermal neutron *S(a,b)* tables within MCNP.

### B. Heavy water replacement

Deuterium was introduced via replacement of hydrogen in the elemental composition of the constituent material(s) of the models. 10% heavy water corresponds to 10% molar replacement of the entire hydrogen content of the material with deuterium. Equilibration of heavy water in areas of the body

with differing permeability, as assumed with the elliptical model, takes place within 2–3 h with a half-life in the body of about 9 days.<sup>11</sup> Thus deuterium replacement in the brain and skull of the elliptical model are in equal proportion.

### C. Dose calculation

Undesirable contaminating radiation such as fast neutrons, reactor core gammas, and structural induced gammas were not included in this calculation. The dose components resulting from such a beam which have been examined separately include

- (1) epithermal neutron dose, principally resulting from  $^1\text{H}(n,n')^1\text{H}$  epithermal neutron scattering reactions,
- (2) thermal neutron dose, resulting from  $^{14}\text{N}(n,p)^{14}\text{C}$  thermal neutron capture reactions,
- (3) tissue induced gamma dose, principally resulting from  $^1\text{H}(n,\gamma)^2\text{H}$  thermal neutron capture reactions, and
- (4) boron-10 dose, resulting from  $^{10}\text{B}(n,\alpha)^7\text{Li}$  thermal neutron capture reactions.

Photon and neutron fluences computed for each tally volume are normalized to per source neutron.<sup>16</sup> These fluences were converted to dose (cGy) per source neutron using fluence to dose conversion factors (KERMA factors<sup>18</sup>).  $^{10}\text{B}$  doses were computed implicitly, i.e.,  $^{10}\text{B}$  was not actually included as part of the brain material composition. These doses were calculated by spectrally integrating neutron fluence convolved with the  $^{10}\text{B}$  KERMA factors. Zamenhof *et al.*<sup>18</sup> have shown that excluding  $^{10}\text{B}$  in such a manner only introduces errors “similar to, or less than, the statistical errors of the Monte Carlo calculations themselves.” In the case of excluding 10  $\mu\text{g/g}$  throughout the entire brain tissue, this introduces an error of approximately 3% in the  $^{10}\text{B}$  dose.<sup>18</sup> (Less than the 5% statistical error criterion set for the calculations in this paper.) Thus the blood boron level (B) chosen for these calculations is 10  $\mu\text{g/g}$ . This is not too excessive to induce significant  $^{10}\text{B}$  dose depression, yet high enough to obtain maximum dose contrast between tumor and healthy tissue.<sup>26</sup>

Tumor  $^{10}\text{B}$  levels ( $T$ ) were taken to vary from 10  $\mu\text{g/g}$  to 100  $\mu\text{g/g}$  to provide a broad coverage over the possible tumor to blood boron range. MCNP calculations by the authors have shown that the inclusion of  $^{10}\text{B}$  at concentrations as high as 100  $\mu\text{g/g}$  in localized volumes of approximately 1  $\text{cm}^3$  introduce a  $^{10}\text{B}$  dose depression of less than 3% within the localized site. This is opposed to the  $^{10}\text{B}$  level in the entire brain volume which causes thermal neutron flux perturbation at levels much lower than 100  $\mu\text{g/g}$ . As such the authors chose to vary the tumor  $^{10}\text{B}$  concentration, yet hold the blood boron level constant. Thus the tumor to healthy tissue dose ratio is maximized via boron levels high enough to produce maximum dose contrast,<sup>26</sup> yet low enough to prevent significant thermal neutron flux perturbation and  $^{10}\text{B}$  dose depression.

Tumor to blood boron ratios ( $T/B$ ) of 1, 2, 3, 4, 5, and 10 are studied with all having a 10  $\mu\text{g/g}$   $^{10}\text{B}$  concentration in the blood. For BPA uptake in humans, the average  $T/B$   $^{10}\text{B}$  ratio is 4.3.<sup>19</sup> For BSH, a  $T/B$   $^{10}\text{B}$  ratio of 1.4 represents an average human uptake.<sup>19</sup> However taking into account the 0.3 capillary dose reduction factor applicable to BSH (Refs.

19, 20, 27) yields an effective  $T/B$   $^{10}\text{B}$  ratio of 4.3. Thus 4.3 is applicable not only to BPA (with  $T=43$   $\mu\text{g/g}$  and  $B=10$   $\mu\text{g/g}$ ) but also to the effective tumor to blood  $^{10}\text{B}$  ratio of BSH (with  $T=43$   $\mu\text{g/g}$ , absolute  $B=30$   $\mu\text{g/g}$ , and effective  $B=10$   $\mu\text{g/g}$ ). Considering the relatively large standard deviations associated with these ratios, the effective tumor to blood boron ratio for BPA and BSH in human patients can only be given as approximately 4–5.

All doses used in this paper are the product of absorbed dose and assumed RBE values. RBE factors, were taken from Zamenhof *et al.*<sup>18</sup> and are as follows:

Radiation type	Recommended RBE
Gamma rays (single dose)	1.0
Thermal neutrons	1.6
Epithermal neutrons	1.6
$^{10}\text{B}$ Reaction	2.3

### D. Definition of NCT dosimetric terminology

Dosimetric criteria and figures of merit have been developed for neutron beam quality and treatment planning. These include

- (1) “advantage depth” (AD)—depth at which dose to tumor equals maximum dose to healthy tissue;<sup>28</sup>
- (2) “therapeutic depth” (TD)—depth at which dose to tumor equals twice the maximum dose to healthy tissue;<sup>14,19</sup>
- (3) “therapeutic ratio” (TR)—ratio of tumor dose to maximum healthy tissue dose.

Maximum healthy tissue dose is considered in the brain volume only, not the skull, as brain capillary endothelia are considered to be the dose limiting tissue. In thermal BNCT, the scalp is the dose limiting tissue. However this is spared by reflection and withdrawal of scalp tissue from the beam.<sup>14,29,30</sup> Thus the depths used in this paper are relative to the brain surface. Advantage depth is equivalent to the maximum usable depth with a therapeutic ratio of 1.0 applied by Zamenhof *et al.*<sup>28</sup> These authors also examine the effect of relaxing the therapeutic ratio to 0.5. In effect, this becomes the depth at which dose to tumor equals half the maximum dose to healthy tissue which is opposed to clinical requirements. This paper examines the effect of a therapeutic ratio of 2.0. Such a restriction results in dose to tumor equal to twice the maximum dose to healthy tissue and is more in line with clinical requirements. As such this figure of merit is termed the “therapeutic depth.”

## III. RESULTS AND DISCUSSION

### A. Thermal beam

Figure 2 displays the advantage depth as measured from the brain surface as a function of  $\text{D}_2\text{O}$  replacement for the 0.025 eV thermal neutron beam. Improvement can be seen as the heavy water concentration rises, however the extent of the increase is dependent upon the  $T/B$  ratio. For a  $T/B$  ratio in the range of 4–5, a clinically feasible 20% heavy water replacement increases the advantage depth by approximately 0.7 cm. Figure 3 shows the therapeutic depth for the thermal beam.  $T/B$  ratios below 3 were unable to give a TR of 2 and thus cannot have a therapeutic depth. For a  $T/B$  in the range

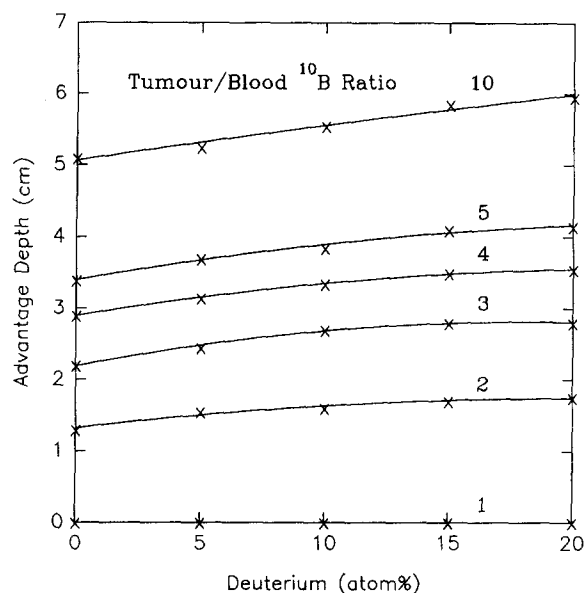


FIG. 2. Advantage depth as a function of D<sub>2</sub>O replacement in the elliptical skull/brain model for the 0.025 eV thermal neutron beam. Curves depicting tumor to blood <sup>10</sup>B ratios of 1, 2, 3, 4, 5, and 10 are shown, all for 10 μg/g blood <sup>10</sup>B concentration.

of 4–5, 20% heavy water replacement increases the TD by approximately 0.4 cm. Thus for shallow tumors, significant gains with thermal neutrons can be made by the relatively simple process of heavy water replacement. Even with 20% heavy water replacement, however, the effective *T/B* required for the therapeutic depth to reach the midline of the

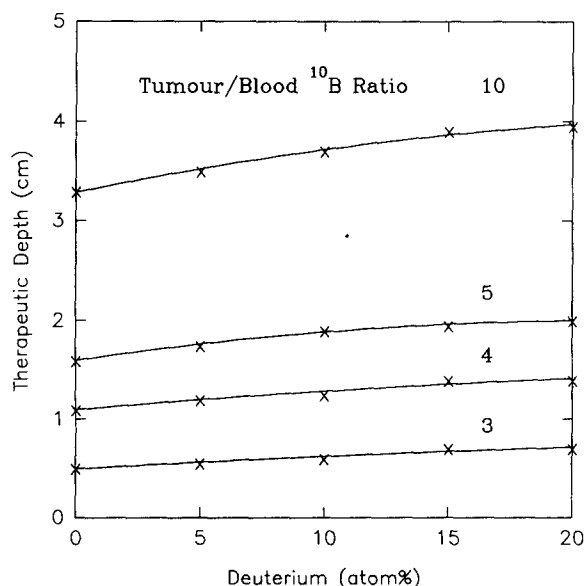


FIG. 3. Therapeutic depth as a function of D<sub>2</sub>O replacement in the elliptical skull/brain model for the 0.025 eV thermal neutron beam. Curves depicting tumor to blood <sup>10</sup>B ratios of 3, 4, 5, and 10 are shown, all for 10 μg/g blood <sup>10</sup>B concentration.

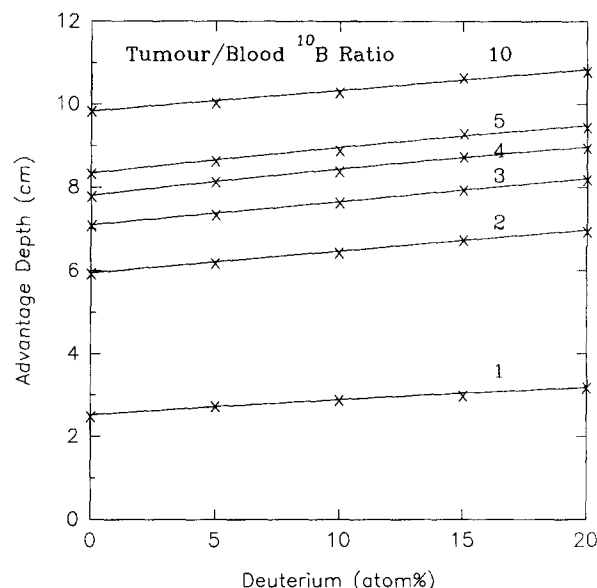


FIG. 4. Advantage depth as a function of D<sub>2</sub>O replacement in the elliptical skull/brain model for the 2–7 keV epithermal neutron beam. Curves depicting tumor to blood <sup>10</sup>B ratios of 1, 2, 3, 4, 5, and 10 are shown, all for 10 μg/g blood <sup>10</sup>B concentration.

brain (6 cm from the brain surface) is of the order of 20. This is far in excess of ratios exhibited by current boron compounds.

## B. Epithermal beam

Figure 4 displays the advantage depth as measured from the brain surface as a function of D<sub>2</sub>O replacement for the 2–7 keV epithermal neutron beam. As for the thermal beam, improvement can be seen as the heavy water concentration rises, however the extent of the increase is dependent upon the *T/B* ratio. For a *T/B* in the range of 4–5, 20% heavy water replacement increases the advantage depth by over 1 cm. Figure 5 shows the therapeutic depth for the epithermal beam. As for the thermal case, *T/B* ratios below 3 were unable to give a TR of 2 and thus cannot have a therapeutic depth. For a *T/B* in the range of 4–5, 20% heavy water replacement increases the TD by over 1 cm to well beyond the midline of the brain.

The effective *T/B* required for the therapeutic depth to reach the midline of the brain is shown in Fig. 6 as a function of heavy water replacement. For 20% replacement, the reduction in the effective *T/B* requirement is from 5.0 to 3.6. Considering the effective <sup>10</sup>B *T/B* measured in humans is of the order of 4–5 for both BPA and BSH, it can be seen that heavy water replacement offers significant improvement for the therapeutic treatment of deep-seated tumors with epithermal neutrons and current generation <sup>10</sup>B drugs. Assuming a worst case scenario of a tumor situated near the midline of the brain, Fig. 7 illustrates depth dose profiles for 0% and 20% D<sub>2</sub>O for the 2–7 keV beam using the average value *T/B* of 4.3.<sup>19</sup> With the 20% heavy water replacement, the <sup>10</sup>B dose component to the tumor has increased due to improved thermal neutron flux penetration. Additionally, the heavy wa-

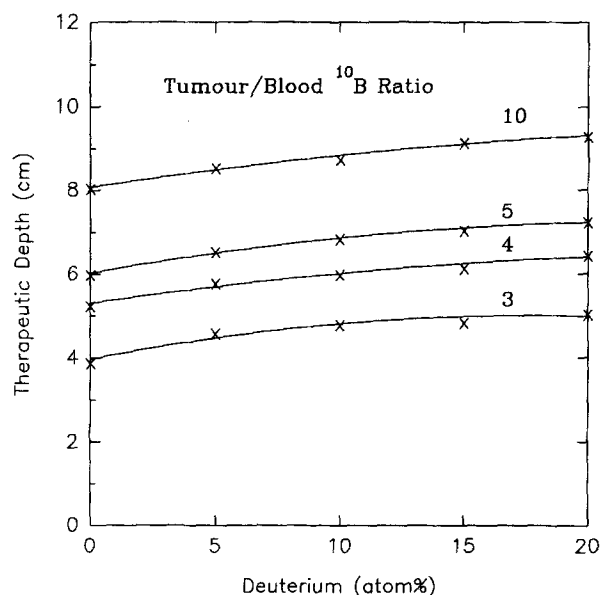


FIG. 5. Therapeutic depth as a function of  $D_2O$  replacement in the elliptical skull/brain model for the 2–7 keV epithermal neutron beam. Curves depicting tumor to blood  $^{10}B$  ratios of 3, 4, 5, and 10 are shown, all for  $10 \mu\text{g/g}$  blood  $^{10}B$  concentration.

ter has the effect of reducing the healthy tissue dose via less induced gammas. This has a twofold effect in improving the therapeutic ratio.

#### IV. CONCLUSION

Heavy water replacement prior to BNCT has the effect of increasing thermal neutron flux penetration and thus dose to

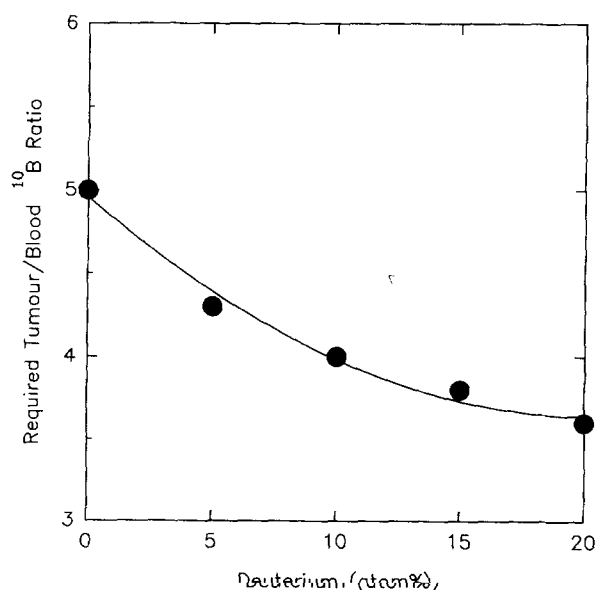


FIG. 6. Effective  $^{10}B$  tumor to blood ratio required for the therapeutic depth to reach the brain midline (6 cm from brain surface) using 2–7 keV epithermal neutrons as a function of heavy water replacement.

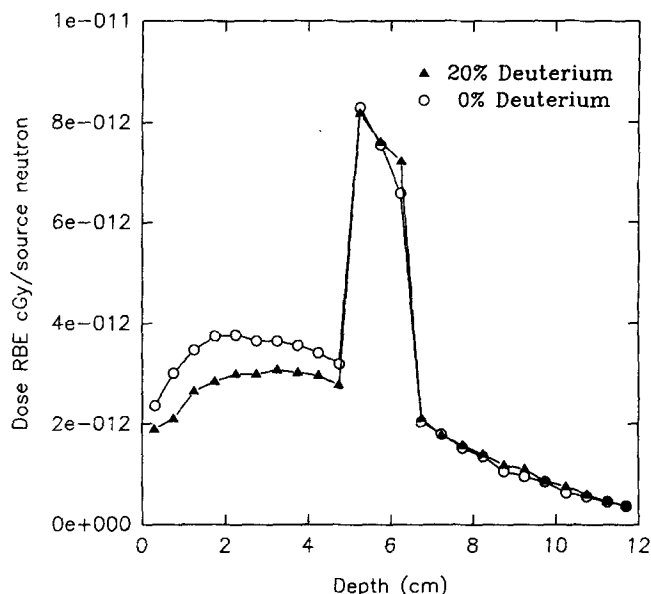


FIG. 7. Dose (RBE cGy/source neutron) along beam axis vs depth for  $10 \mu\text{g/g}$  blood  $^{10}B$  and  $43 \mu\text{g/g}$  tumor  $^{10}B$  ( $T/B=4.3$ )—tumor site 5.25–6.25 cm from brain surface. Dose profiles for the 2–7 keV epithermal beam are shown for 0% and 20% heavy water replacement. The boron dose component to the tumor is increased with heavy water present due to improved neutron flux penetration. Healthy tissue dose is also reduced due to less induced gammas. This study has only 0.5 cm resolution. The transition from tumor to healthy tissue dose is expected to be much sharper.

tumor cells while lowering the healthy tissue dose via reduced induced gammas. Using the MCNP transport code with an elliptical skull/brain model, the parameters of advantage depth and therapeutic depth were studied as a function of  $D_2O$  replacement. Analysis was performed for tumor to blood  $^{10}B$  ratios in the range 1–10 with  $10 \mu\text{g/g}$  in the blood. For thermal neutrons, 20% heavy water replacement extended the advantage depth by approximately 0.7 cm and the therapeutic depth by approximately 0.4 cm for an effective tumor to blood  $^{10}B$  ratio in the range of 4–5 (average range of BSH and BPA). The  $T/B$  required for the therapeutic depth to reach the midline of the brain is of the order of 20 even with 20% heavy water replacement. Thus for shallow tumours, significant gains with thermal neutrons can be made by the relatively simple process of heavy water replacement. It must be stated, however that the financial cost of such quantities of heavy water is not insignificant.

Improvement in epithermal beam parameters can be seen as the heavy water concentration rises, with the extent of the increase dependent upon the  $T/B$  ratio. For a  $T/B$  in the range of 4–5, 20% heavy water replacement increases the advantage depth and the therapeutic depth by over 1 cm to well beyond the midline of the brain. The effective  $T/B$  required for the epithermal therapeutic depth to reach the midline of the brain reduces from 5.0 to 3.6 with 20% heavy water replacement. These requirements would certainly be increased if fast neutron and gamma ray contamination of the beam were considered in the calculation. Considering the effective  $^{10}B$   $T/B$  measured in humans is of the order of 4–5

for both BPA and BSH, it can be seen that heavy water replacement offers significant benefit for the therapeutic treatment of deep-seated tumors with epithermal neutrons and current generation  $^{10}\text{B}$  drugs.

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