

ORIGINAL RESEARCH ARTICLE

Isoeffective dose prescription in boron neutron capture therapy

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Abstract

How to prescribe doses in boron neutron capture therapy (BNCT) remains controversial. Dose components in BNCT should be prescribed so that their biological effects are equivalent to those produced by reference photon doses in conventional radiotherapy, for which the dose–effect relationship is well understood because of the very large body of accumulated data and experience. For too many years, the “equivalent” gamma dose has been obtained from the boron and neutron doses by multiplying them by fixed weighting factors and adding them together. This simple additive procedure has been proven erroneous; it significantly overestimates the dose given to the tumor and underestimates the dose to healthy tissue, giving rise to potentially hazardous situations. An alternative is the isoeffective approach, which accounts for the nonlinear relationship between the reference photon dose required to produce a given biological effect and the high- and intermediate-linear-energy-transfer BNCT dose components, namely the boron- and neutron-related doses, required to produce the same effect. Here, we review the current state of the art and provide further support for this approach. As an application of these concepts, we analyze the performance of the Buenos Aires BNCT beam shaping assembly, showing the important consequences of adopting the second alternative.

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1. Introduction

Boron neutron capture therapy (BNCT) is gaining significant momentum worldwide following the development of accelerator-based systems suitable for installation in hospitals. BNCT delivered using such accelerator systems is termed accelerator-based BNCT (AB-BNCT).¹

A major unsettled issue in BNCT is how to prescribe doses to both the tumor and dose-limiting normal tissues, such as healthy brain (HB) in the treatment of central nervous system tumors.¹⁻³ In this context, dose prescription must balance the dose required to achieve an acceptable probability of tumor control against the dose tolerated

by normal tissue. For normal-tissue evaluation, we use the equivalent uniform dose (EUD), which can be related to the probability of adverse effects (see **Section 2.4**).

We need a reliable methodology to convert the high- and intermediate-linear-energy-transfer (LET) components of BNCT into doses that are truly dose–effect equivalent to the well-known gamma-radiation dose, D_γ (i.e., conventional radiotherapy), for which extensive databases and substantial accumulated experience are available regarding the doses necessary to control different tumors. Throughout this paper, the terms “gamma” and “photon” are used interchangeably. These BNCT dose components include: (i) α particles and ^7Li ions produced by the $^{10}\text{B}(n,\alpha)^7\text{Li}$ capture reaction after delivery of ^{10}B by boronophenylalanine (BPA) or another boron carrier, with the associated dose denoted by D_b ; and (ii) recoil protons from elastic collisions, $^1\text{H}(n,n')^1\text{H}$, with fast neutrons ($E_n \geq 10$ keV), together with protons and ^{14}C recoils from the $^{14}\text{N}(n,p)^{14}\text{C}$ capture reaction ($E_p \approx 583$ keV), with the corresponding dose denoted by D_n . As a simplifying assumption, we combine the doses from fast recoil protons and the $^{14}\text{N}(n,p)^{14}\text{C}$ capture reaction (denoted D_n) because their radiobiological effects are considered sufficiently similar for a first-order approximation. Such a methodology, which is discussed in the present paper, has important predictive value for the outcome of BNCT treatment.

For many years, there has been a widespread tendency to use fixed values, the so-called relative biological effectiveness (RBE) factors, for a given radiation quality and biological endpoint. RBE is defined as the ratio of the physical dose of gamma (or photon) radiation to the physical dose of the radiation in question that produces the same effect, e.g., $\text{RBE}_{n,1\%} = D_{\gamma 1\%}/D_{n,1\%}$ for neutrons. Specification of the effect level is essential because RBE depends strongly on the biological endpoint and effect level; therefore, no single RBE value is universally applicable. Such RBE and CBE values are often used as weighting factors and are used to obtain the corresponding gamma doses that should have the same biological effect and are therefore termed “equivalent” doses. By simply multiplying the physical doses of the high- and intermediate-LET components by fixed RBE/CBE weighting factors and summing the resulting weighted components, an “equivalent” gamma dose is obtained that is intended to represent a conventional radiotherapy dose producing the same biological effect.

The RBE for boron is called compound biological effectiveness (CBE_b) because it additionally depends on the specific boron carrier and its microdistribution at the cellular and tissue levels. Frequently, RBE values associated with a 1% survival fraction (SF) in cell cultures of different

cell lines representing different tumor types, or with other biological endpoints, have been adopted. Values associated with 10% or even 50% survival have also been adopted. However, no single SF level has a uniquely privileged biological basis. These constant values are presented in **Table 1**.

2. Materials and methods

2.1 “Equivalent” versus isoeffective procedures

There is neither a logical nor an empirical basis for treating the values in **Table 1** as universally valid (i.e., under all conditions). CBE and RBE values often depend strongly on the SF or other biological endpoint and on the reference radiation. Moreover, the survival levels required for tumor control can be substantially below 1%, and these values also depend on the reference radiation (for examples illustrating the dependence of CBE and RBE on SF, see Refs.^{1–3}). The use of fixed RBE and CBE factors leads to unrealistic weighted/equivalent dose values compared with the photon doses known to be necessary to control tumors or to avoid unacceptable normal-tissue toxicity. It systematically leads to substantial overestimation of the predicted equivalent tumor dose (by up to a factor of two) and underestimation of the predicted equivalent dose to healthy tissue. Both effects are misleading and potentially dangerous.

Table 1. Constant weighting factors used in the literature to convert BNCT dose components into equivalent gamma doses

Tissue type	CBE_b or weight	RBE_n or weight	RBE_γ
Tumor	3.8	3.2	1
Healthy brain	1.3	3.2	1

Notes: The boron carrier is BPA. The RBE_n factor of 3.2 was determined from normal-brain irradiation in dogs, whereas the CBE_b value was determined using a rat spinal cord model. The photon reference radiation was 100-kV X-rays in Ref.⁴, in contrast to the megavoltage photons used in Ref.⁵, which are more compatible with the gamma-ray energies present in BNCT.

Abbreviations: BNCT: Boron neutron capture therapy; BPA: Boronophenylalanine; CBE_b : Compound biological effectiveness factor for boron; RBE_n : Relative biological effectiveness factor for neutrons; RBE_γ : Relative biological effectiveness factor for gamma rays.

Hence, a well-defined mathematical procedure is needed to map the BNCT dose components onto the D_γ values corresponding to tumor control or the maximum tolerable doses to organs at risk, such as the skin, mucosa, or HB. The isoeffective procedure provides such a framework.^{1,2} The conventional procedure is intended to represent the same isoeffective principle but fixes RBE/CBE weighting

factors at values associated with predetermined endpoints and assumes simple additivity (see **Equation 1**). This isoeffective methodology has been applied to melanoma², glioblastoma multiforme (GBM)^{6,7}, head and neck (H&N) cancers^{8,9}, and osteosarcoma.¹⁰

The “equivalent” or RBE dose is given by **Equation 1**, where D_γ^b is the gamma component of the BNCT beam:

$$D_w \text{ (or RBE-Dose)} = CBE_B \cdot D_B + RBE_n \cdot D_n + D_\gamma^b \quad (1)$$

The isoeffective dose is given by **Equation 2**:

$$D_{iso}(D_B, D_n, D_\gamma^b) = -0.5(\alpha_\gamma / \beta_\gamma) + [0.25(\alpha_\gamma / \beta_\gamma)^2 + \Sigma / \beta_\gamma]^{1/2} \quad (2)$$

This expression can also be written in terms of the ratios of all parameters to α_γ :

$$D_{iso}(D_B, D_n, D_\gamma^b) = 0.5(\alpha_\gamma / \beta_\gamma) [-1 + [1 + 4 / (\alpha_\gamma / \beta_\gamma)(\Sigma / \alpha_\gamma)]^{1/2}] \quad (3)$$

where

$$\Sigma / \alpha_\gamma = (\alpha_B / \alpha_\gamma) D_B + (\alpha_n / \alpha_\gamma) D_n + D_\gamma^b + (\beta_\gamma / \alpha_\gamma) D_\gamma^{b2} \quad (4)$$

Σ is called the “effect” and D_B , D_n , and D_γ^b are the physical BNCT dose components. The ratios α_B / α_γ and α_n / α_γ are denoted A_B and A_n , respectively.

This is a simplified version of the complete isoeffective procedure, in which the effect in the BNCT case, in addition to the linear terms in the different doses (D_B , D_n , and D_γ^b), includes a full quadratic form with diagonal terms $\beta_B D_B^2$ and $\beta_n D_n^2$ and so-called synergistic terms^{1,2} representing the simultaneous action of two different radiations: $2(\beta_B \beta_\gamma)^{1/2} D_B D_\gamma^b$, $2(\beta_n \beta_\gamma)^{1/2} D_n D_\gamma^b$, and $2(\beta_B \beta_n)^{1/2} D_B D_n$.

For simplicity, and as is often the case, we have adopted $\beta_B = \beta_n = 0$ for the high- and intermediate-LET radiation components (boron and neutron, respectively) throughout most of this paper, except where otherwise stated. However, to assess the robustness of the results, we have also calculated the full expressions whenever the corresponding experimentally determined β values are nonzero. For the tumor in particular, the influence of these terms is quite small (see the first row of **Table 2**). The isoeffective dose is dominated by the boron dose.

The α and β parameters are the usual radiobiological parameters for each type of radiation in the linear-quadratic model. **Equations 2 and 3** give the positive solution to the following quadratic equation:

$$\alpha_\gamma D_\gamma + \beta_\gamma D_\gamma^2 = \alpha_B D_B + \alpha_n D_n + \alpha_\gamma D_\gamma^b + \beta_\gamma D_\gamma^{b2} \quad (5)$$

The right-hand side of **Equation 5** can also be written, by factoring out D_B , as:

$$D_B [\alpha_B + \frac{\alpha_n D_n}{D_B} + \frac{\alpha_\gamma D_\gamma^b}{D_B} + \beta_\gamma D_B \left(\frac{D_\gamma^{b2}}{D_B^2} \right)] \quad (6)$$

Here, $D_\gamma (= D_{iso})$ is the isoeffective gamma dose, and the doses on the right-hand side are the corresponding physical doses delivered by the BNCT neutron beam. The ratios $\frac{D_n}{D_B}$ and $\frac{D_\gamma^b}{D_B}$ must be determined for the specific beam and treatment system and are independent of beam intensity. D_γ^b is the gamma component present in BNCT, arising partly from radiative capture in tissue hydrogen and partly from photon contamination associated with the incident beam and beam shaping assembly (BSA). **Equation 5** equates the exponent of the gamma-reference

Table 2. Physical BNCT dose components and derived weighted and isoeffective photon doses for tumor and HB tissue using the Buenos Aires AB-BNCT system and BSA (TT = 62 min)

Tissue	Physical dose components in BNCT beam (Gy)					D_w (Gy)	D_{iso} (Gy)
	$^{10}\text{B}(\text{n},\alpha)^7\text{Li}$	$^1\text{H}(\text{n},\text{n}')^1\text{H}$	$^{14}\text{N}(\text{n},\text{p})^{14}\text{C}$	Gamma	Total	Total	Total
Tumor	13.90	0.21	0.39	3.89	18.39	58.63	41.48–41.82
HB average	1.34	0.12	0.13	1.24	2.83	3.78	7.75–8.21
HB max	3.93	0.29	0.39	3.71	8.32	11.00	14.11–16.33
HB EUD	2.71	0.21	0.27	2.55	5.74	7.61	11.47–12.77
HB EUD reduced	1.64	0.13	0.16	1.55	3.48	4.62	8.64–9.27

Notes: D_w values were obtained using **Equation 1** and the weighting factors given in **Table 1**. D_{iso} values were obtained using **Equations 2 and 3** and the radiobiological coefficients α and β (or A and B) given in **Table 4**. For HB, $\alpha_\gamma / \beta_\gamma = 2$ was adopted from Ref.¹¹ The two values in the final column were calculated without and with the β_B and β_n terms, respectively. The last two rows give the EUD values calculated using **Equation 9**, with the weighting factors $\omega_1 = 0.47$ and $\omega_2 = 0.53$ for a single irradiation field. The final row gives the reduced values corresponding to a stereotactic radiosurgery (SRS) photon dose of 31.4 Gy and TT = 37.5 min. Abbreviations: AB-BNCT: accelerator-based boron neutron capture therapy; BNCT: boron neutron capture therapy; BSA: beam shaping assembly; EUD: equivalent uniform dose; HB: healthy brain; SRS: stereotactic radiosurgery; TT: treatment time.

survival curve to the combined exponent of the product of the SFs for the radiations present in BNCT, reflecting the multiplicative nature of the survival probabilities. These exponents are generically called “effects.” **Equation 5** can be used to determine D_B , provided that the ratios of D_n and D_γ^b to D_B , which are independent of beam intensity, have been determined experimentally, if the $D_\gamma = D_{iso}$ required to control the tumor is known. Conversely, **Equation 5**, through **Equation 2 or 3**, can be used to calculate D_{iso} if the dose components of the BNCT beam are known.

We have neglected the Lea–Catcheside time factors^{1,2,12} related to sublethal damage repair. The single-session treatment times (TTs) considered were 62 min and 37.5 min for the reference and reduced cases, respectively. The fast repair time constants for GBM and HB are 91 min and 42 min, respectively^{6,11}; for these treatment times and repair constants, the corresponding Lea–Catcheside correction factors range from 0.8 to 1. The energy of the reference gamma radiation should be as close as possible to that of the gamma radiation, D_γ^b , present in BNCT,⁴ so that the same α_γ and β_γ values can be used for D_γ and D_γ^b .

It is interesting to note that these two procedures, represented by **Equation 1** and **Equations 2 or 3**, converge to the same result at very low doses when the quadratic term in the gamma “effect” expression, $\alpha_\gamma D_\gamma + \beta_\gamma D_\gamma^2$, can be neglected. Mathematically, this condition can be expressed as $\beta_\gamma D_\gamma^2 \ll \alpha_\gamma D_\gamma$, which implies $D_\gamma \ll \alpha_\gamma / \beta_\gamma$. However, this condition lies far below the therapeutically useful range, as will be shown explicitly later for both HB and GBM. Only under this condition is **Equation 1** valid, giving $CBE_B = \alpha_B / \alpha_\gamma$ and $RBE_n = \alpha_n / \alpha_\gamma$. At higher gamma doses, however, D_w is substantially larger than D_{iso} . As already noted, this overestimation is misleading.

2.2 Discussion of a numerical example

Consider a numerical example to illustrate this point.

Suppose that $\alpha_B = 3$, $\alpha_n = 1$, $\beta_B = \beta_n = 0$, $\alpha_\gamma = 0.21$, and $\beta_\gamma = 0.07$ ($\alpha_\gamma / \beta_\gamma = 3$). Once the radiobiological parameters have been specified, all other quantities can be calculated.

For a given SF, the boron component is described by $SF = \exp(-\alpha_B D_B)$ and hence $D_B = \ln(SF^{-1}) / \alpha_B$. For the neutron component alone, the corresponding expression is $SF = \exp(-\alpha_n D_n)$. For the reference photon radiation, $SF = \exp[-(\alpha_\gamma D_\gamma + \beta_\gamma D_\gamma^2)]$, from which D_γ can be obtained (using **Equation 2** and substituting Σ for $\ln(SF^{-1})$). For simplicity, we omit the gamma component D_γ^b associated with the BNCT beam. To illustrate the difference between the equivalent dose D_w and the isoeffective dose D_{iso} , **Table 3** shows the doses, CBE values, and RBE values for SFs of 1% and 0.1%. Even at these dose levels, which are below the therapeutic doses, the D_w values are substantially larger than the corresponding D_{iso} values.

2.3. Requirements for facility characterization and dose prescription

In light of the preceding discussion, we briefly outline some of the points that should be considered when setting up a BNCT procedure in a treatment facility and obtaining the information necessary for dose prescription:

- (i) For each AB-BNCT facility, including the BSA and treatment room, the neutron spectrum must be characterized as comprehensively and accurately as possible through measurements and simulations. This can be accomplished using different methods, e.g., multi-foil activation measurements covering the complete energy range or other types of detectors. The associated dose components delivered by the beam should preferably be determined within anthropomorphic phantoms. The neutron and gamma doses should be measured without boron, whereas the boron dose can be determined by simulating a tumor with the measured or inferred boron concentration. In addition, the gamma spectrum associated with the neutron beam and patient environment should be characterized, and the associated photon contamination and dose should be minimized through appropriate shielding. The fast-neutron component (neutron energies, $E_n \geq 10$ keV) and thermal component ($E_n \leq 0.5$ eV) should be kept as

Table 3. Gamma, boron, and neutron doses; CBE values for boron; RBE values for neutrons; and “equivalent” and isoeffective gamma doses for SF values of 1% and 0.1%

SF (%)	D_γ (Gy)	D_B (Gy)	D_n (Gy)	CBE_B	RBE_n	D_w (Gy)	D_{iso} (Gy)
1	6.75	1.54	4.61	4.38	1.46	13.49	10.07
0.1	8.55	2.30	6.91	3.72	1.24	17.09	12.63

Notes: For this example, $\alpha_B = 3$, $\alpha_n = 1$, $\beta_B = \beta_n = 0$, $\alpha_\gamma = 0.21$, and $\beta_\gamma = 0.07$ ($\alpha_\gamma / \beta_\gamma = 3$). For simplicity, the gamma component D_γ^b associated with the BNCT beam is omitted. The D_w values are substantially higher than the corresponding D_{iso} values.

Abbreviations: BNCT: boron neutron capture therapy; CBE: compound biological effectiveness; RBE: relative biological effectiveness; SF: survival fraction.

low as possible at the patient entrance (skin and skull); a pure epithermal beam would be ideal. With these data, the doses delivered to the different tissues and the entire irradiated volume can be simulated using an appropriate Monte Carlo transport code.

- (ii) For different types of cancer, such as GBM and H&N, cell lines derived from these tumor types should be characterized radiobiologically through clonogenic assays at the facility. They may also be implanted in animal models to provide a more physiologically relevant *in vivo* model of the clinical radiotherapy setting. This involves measuring survival curves (or other biological endpoints) and determining the α and β parameters, both with the neutron beam alone and with boron-loaded cells or tissues. The specific cell lines should be characterized radiobiologically using reference gamma radiation with an energy as close as possible to that of the gamma radiation present in the treatment beam.⁶ It has been shown that the radiobiological parameters (α_γ and β_γ) obtained with 250-kVp X-rays, with mean gamma energies of approximately 80–100 keV, differ substantially from those obtained using higher-energy reference photons such as ⁶⁰Co rays or megavoltage X-rays from linear accelerators. Both the mean cellular boron concentration and, where feasible, its subcellular microdistribution (e.g., between the nucleus and cytoplasm) should be measured to enable correlation with α_B . The different doses to be delivered should be carefully simulated and measured.
- (iii) A protocol should be developed to maximize the boron concentration in tumor tissue in patients (infusion strategy). Every effort should be made to determine this concentration *in vivo*, ideally using BPA positron emission tomography and real-time monitoring with dedicated BNCT single-photon emission computed tomography (SPECT) to measure the 478-keV gamma ray released in the ¹⁰B(n, α)⁷Li capture reaction. If SPECT or another real-time boron-monitoring modality is unavailable, blood boron concentration will need to be measured, together with the available information on the tumor-to-blood and tumor-to-normal tissue boron concentration ratios. This information is essential for calculating or simulating, for a given neutron beam, the dose associated with the boron capture reaction and, e.g., the irradiation time necessary to deliver the required boron dose.
- (iv) The boron dose, together with the other accompanying doses, should be determined as that producing the appropriate isoeffective reference gamma dose (see discussion above). This gamma dose should be derived from data available for patients treated with photons in

single-session treatments, such as SRS, delivered over a similarly short treatment duration to the intended BNCT treatment.⁵ Bunevicius *et al.*⁵ analyzed patients treated with SRS and showed that, with a single fraction of 31.4 ± 7.2 Gy, local control, defined as complete response, partial response, or stable disease, reached 68%. For instance, taking 31.4 Gy as the reference gamma dose, and hence as the isoeffective dose to be adopted, we obtain approximately 8.4 Gy for the physical boron dose, D_B (with $\alpha_B = 3.0$ and BPA; see Ref.⁶). From this boron dose, the necessary irradiation time for a given facility can be calculated.

The procedures described above may yield a starting point or first approximation for rational dose prescription, given the numerous uncertainties, particularly the differences between *in vitro* and *in vivo* radiobiological parameters, the inhomogeneity of boron distribution across tumor and healthy tissues, and the energy dependence of the radiobiological parameters. The dose prescription may then be optimized as more data on treatment outcomes become available.

2.4. Radiotoxic effects of boron neutron capture therapy in the healthy brain

The preceding sections focus primarily on tumor-dose prescription; however, the effects of BNCT on normal tissue must also be considered.

This issue was discussed in detail recently¹¹, so we briefly summarize the most important points. The discussion focused on the normal tissue complication probability (NTCP) for HB.

The NTCP as a function of dose, D , can be represented mathematically as:

$$NTCP(D) = \left(1 / \sqrt{2\pi}\right) \cdot \int_{-\infty}^{S(D)} e^{-t^2/2} dt \quad (7)$$

where $S(D) = (D - TD_{50}) / (m \cdot TD_{50})$.

TD_{50} is the dose associated with a 50% probability of developing the complication, and m determines the slope of the NTCP as a function of D at $D = TD_{50}$. This slope is given by $(m \cdot TD_{50} \cdot \sqrt{2\pi})^{-1}$.

Equation 7 is applicable to both single-fraction photon irradiation with a uniform dose D and to BNCT, where $D = D_{iso}(D_B, D_n, D_\gamma^b)$, as given by **Equations 2 or 3**. The radiobiological parameters involved in **Equations 2 and 7** were determined retrospectively by analyzing the rate of limb paralysis in the rat spinal cord after BNCT and photon irradiation using data from irradiations performed at the Brookhaven Medical Research Reactor.¹³

In addition, somnolence syndrome was considered an adverse effect in the HB after both photon radiotherapy¹⁴ and BNCT. A retrospective analysis was performed using data from patients with malignant gliomas enrolled in clinical trials with BPA conducted at Helsinki Central Hospital between 2001 and 2008.¹⁵

Because a large volume of HB is irradiated during the treatment of malignant gliomas and other cancer types, it is important to determine which dose metric is relevant for correlation with adverse effects. Photon radiotherapy involves relatively uniform dose distributions in the brain, and therefore the volume of irradiated tissue is an important factor in the occurrence of side effects.¹⁶ The occurrence of somnolence syndrome after BNCT has also been reported.⁴ However, whole-brain dose distributions after BNCT are nonuniform, and neither average whole-brain doses nor peak doses to a 1-cm³ volume predict the development of this adverse effect.^{4,17} Therefore, as indicated by Coderre *et al.*⁴, these dose measures should be used with caution when compared with data from more uniform photon irradiation.

To address this problem, the concept of EUD was developed.¹⁸ EUD is a generalized average defined as:

$$EUD = \left[\sum v_i D_i^a \right]^{1/a} \quad (8)$$

where the summation is performed over all nonoverlapping subvolumes; v_i is the fractional volume of subvolume i , within which the dose D_i is assumed to be approximately uniform. Together, the subvolumes comprise the entire irradiated HB. The model parameter “ a ” is specific to the organ under consideration. Following the whole-brain EUD parameterization used in Ref.¹⁹, we set $a = 10$.

If the whole-brain dose distribution is unavailable, EUD can be obtained as a weighted average of the average dose D_{av} and the maximum dose D_{max} , as shown previously¹¹:

$$EUD = \omega_1 D_{av} + \omega_2 D_{max} \quad (9)$$

where $\omega_1 + \omega_2 = 1$. These weights depend on the number of irradiation fields.¹¹ For a single field, $\omega_1 = 0.47$ and $\omega_2 = 0.53$. These values are used hereafter.

Single-fraction gamma doses associated with a 50% probability of grade ≥ 2 somnolence range from 11.3 to 13.2 Gy.¹¹ These values are of a similar magnitude to the reported EUD range of 10.1–11.3 Gy.¹¹

These results show that the weighted doses D_w are substantially lower than the isoeffective ones represented by the EUD values. This underestimation is potentially dangerous because it may lead to the mistaken conclusion that the biologically equivalent dose is lower than indicated

by the isoeffective estimate.

3. Results and discussion

We analyzed the performance of the Buenos Aires AB-BNCT system and its BSA for the treatment of GBM using the isoeffective procedure for dose estimation.

The Buenos Aires BSA, described in Ref.²⁰, is shown in Figure 1. This BSA includes all standard components: a moderator, a neutron reflector, fast-neutron and gamma shielding, and a collimator. The moderator (cyan) consists of alternating AlF_3 and Al layers. The neutron reflector and gamma shield are made of lead (gray), whereas the fast-neutron shield is made of lithiated polyethylene (yellow). The collimator is composed of lead and lithiated polyethylene.

The original optimization of the geometry was performed under the following constraints. Following common practice, Gy-Eq units were used, denoting the RBE/CBE-weighted dose calculated using Equation 1. The physical dimension of all doses is Gy because the RBE and CBE values are dimensionless. The constraints were as follows: (i) $D_{brain}(d) \leq 11.0$ Gy-Eq, regardless of the depth, d , in the patient's head, calculated from the head surface along the beam axis, where $D_{brain}(d)$ is the dose deposited in HB tissue at depth d ; and (ii) $D_{skin} \leq 16.7$ Gy-Eq, where D_{skin} is the dose deposited in the scalp. The TT was determined when the upper limit of the first constraint was reached while the second constraint remained satisfied. The deuteron beam current was 30 mA.

The radiobiological parameters used for both GBM⁶ and HB¹¹ are shown in Table 4.

The neutron source was a thick ^{13}C target irradiated via the $^{13}C(d,n)$ reaction with 1.5-MeV deuterons, with a yield of 1.9×10^{11} n/mC. The angular and energy distributions were adopted from Ref.²¹ The patient's head was modeled using a modified Snyder phantom.²² The tissue compositions of the patient's head were based on ICRU Report 46²³ and were modified to include 22.5 $\mu\text{g/g}$, 0 $\mu\text{g/g}$, and 15 $\mu\text{g/g}$ of ^{10}B in the scalp, skull, and HB, respectively. For neutron dose calculations, the ^{10}B concentration was 52.5 $\mu\text{g/g}$.

Under these conditions, the TT was 62 min, and the maximum equivalent dose to the tumor was 58.63 Gy-Eq (or RBE-Gy), whereas the maximum equivalent dose to HB was 11.00 RBE-Gy. The equivalent or RBE dose was calculated using the conventional RBE and CBE values: $RBE_n = 3.2$, $CBE_B(BPA) = 3.8$, and $RBE_\gamma = 1$ for the tumor, and $RBE_n = 3.2$, $CBE_B(BPA) = 1.3$, and $RBE_\gamma = 1$ for the HB. The physical boron dose was 13.9 Gy for the tumor, whereas the average and maximum HB boron doses were 1.34 and 3.93 Gy, respectively.

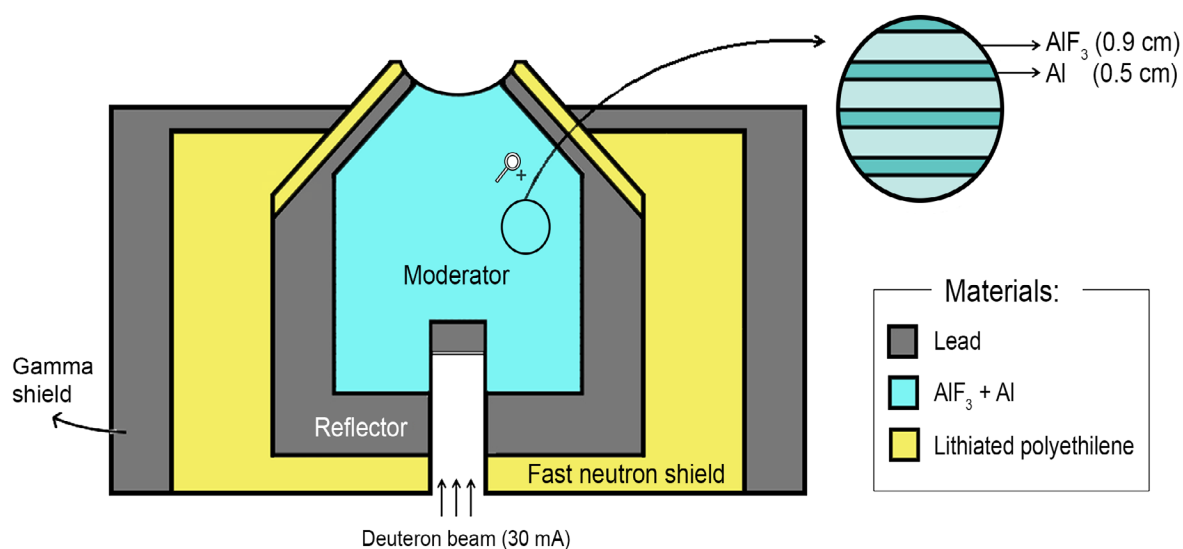


Figure 1. Structure of the Buenos Aires beam shaping assembly. Figure created by the authors with MCNPX visual editor and Photoshop based on information from Ref.²⁰

The physical dose components for the tumor and for the average and maximum HB exposures are shown in Table 2, together with the corresponding D_w and D_{iso} values. D_w values were obtained using Equation 1 and the weighting factors given in Table 1. D_{iso} values were obtained using Equations 2 or 3 and the radiobiological coefficients α and β (or A and B) given in Table 4. We adopted $\alpha/\beta_\gamma = 2$ Gy for HB from Ref.¹¹

The two D_{iso} values in the last column of Table 2 correspond, respectively, to an approximation that neglects the β_B and β_n terms and to a calculation that includes them. For the tumor, the β_n terms are $\beta_n(D_n)^2 + 2(\beta_n \beta_\gamma)^{1/2} D_n D_\gamma$, whereas the corresponding β_B terms are included for the HB case (Table 4).^{1,2,11}

Table 4. Radiobiological parameters for GBM⁶ and HB¹¹

Parameter	Gamma	Neutron	Boron
α [Gy ⁻¹] for GBM	0.21	0.5	3.0
β [Gy ⁻²] for GBM	0.02	0.5	0
α_x/α_γ for HB	1.0	36	20
β_x/α_γ [Gy ⁻¹] for HB	0.5	0	1

Notes: For HB, the ratios of the α and β parameters for radiation component X (X = B, n, or γ) to α_γ are given. The α/β_γ ratio is 10.5 Gy for GBM and 2 Gy (or 3 Gy) for HB. These parameters were obtained using reference gamma radiation with an energy similar to that of the megavoltage photons used in Ref.⁵

Abbreviations: GBM: glioblastoma; HB: healthy brain.

When the isoeffective procedure¹⁻² is used together with the concept of EUD¹⁸ to evaluate the limiting dose to HB under the same conditions described above, we obtain $EUD(D_w) = 7.61$ Gy and $EUD(D_{iso}) = 11.47$ Gy without β_B terms or 12.77 Gy with quadratic β_B terms included. These results show that the conventional weighted-dose procedure substantially underestimates the dose to HB. To obtain the EUD values, we used the weighting factors for a single irradiation field, namely $\omega_1 = 0.47$ and $\omega_2 = 0.53$.

For the tumor, at the maximum dose located at a depth of 2 cm and using the radiobiological parameters obtained for GBM in Ref.⁶, D_{iso} was 41.48 Gy without β_n terms and 41.82 Gy with β_n terms. These values show that the conventional method substantially overestimates the tumor dose, which was calculated as 58.63 Gy using the weighted-dose approach.

Using the isoeffective procedure for the boron dose and taking 31.4 Gy as the reference dose for single-fraction SRS, corresponding to a local control rate of 68%⁵, we obtain a physical boron dose of 8.43 Gy instead of the 13.90 Gy obtained in the original calculation. This calculation includes the quadratic and cross-interaction terms retained in the full model. The revised dose is approximately 0.61 times the original value, corresponding to a reduction of approximately 39% and a TT of 37.5 min. Under these conditions, $EUD(D_{iso})$ for HB is 9.27 Gy, which remains below the lower end of the 11.3–13.2 Gy range associated with a 50% probability of grade ≥ 2 somnolence.¹¹ This result may allow further optimization of the BSA.

Finally, the ratio α/β is 10.5 Gy for GBM and 2 Gy (or 3 Gy) for HB. These values do not satisfy the condition $D_{\gamma} \ll \alpha/\beta$, that would allow the quadratic term in the gamma-radiation effect to be neglected, because D_{γ} is 31.4 Gy for the single-fraction photon dose used in GBM SRS and approximately 9 Gy for the EUD in HB.

4. Conclusion

This paper reviews the methods to prescribe BNCT doses so that their biological effects can be related to those of the megavoltage gamma radiation used in conventional radiotherapy. We review and present scientific evidence and arguments supporting the isoeffective procedure over the conventional “equivalent” procedure. We present a mathematical expression that defines the dose range in which the two procedures yield the same result; this range is far below the therapeutically useful range. In particular, we emphasize that the customary fixed-weighting-factor method for prescribing “equivalent” doses, which is frequently used in the literature, leads to substantial overestimation of the tumor dose and underestimation of the dose to HB. Through analysis of the performance of the Buenos Aires BSA design, we show how the isoeffective procedure substantially changes the conclusions obtained using the traditional approach.

Finally, we emphasize that the isoeffective dose values presented here (Table 2) are only first approximations of the values applicable to actual treatment. Although they are theoretically and empirically well grounded, uncertainties and simplifications remain in the determination of the radiobiological parameters.

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Conflict of interest

The authors declare that they have no competing interests.

Author contributions

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Availability of data

Additional data can be obtained from the corresponding author upon request.

References

1. International Atomic Energy Agency. *Advances in Boron Neutron Capture Therapy*. Vienna, Austria: International Atomic Energy Agency; 2023. CRCP/BOR/002.
2. González SJ, Santa Cruz GA. The photon-isoeffective dose in boron neutron capture therapy. *Radiat Res*. 2012;178(6):609–621.
doi: 10.1667/RR2944.1
3. Kreiner AJ. From the atomic nucleus to cancer cure: The marvel of BNCT a nuclear physicist views. Achievements and outstanding problems. *Appl Radiat Isot*. 2025;220:111725.
doi: 10.1016/j.apradiso.2025.111725
4. Coderre JA, Hopewell JW, Turcotte JC, *et al*. Tolerance of normal human brain to boron neutron capture therapy. *Appl Radiat Isot*. 2004;61(5):1083–1087.
doi: 10.1016/j.apradiso.2004.05.009
5. Bunevicius A, Pikis S, Kondziolka D, *et al*. Stereotactic radiosurgery for glioblastoma considering tumor genetic profiles: an international multicenter study. *J Neurosurg*. 2022;137(1):42–50.
doi: 10.3171/2021.7.JNS211277
6. Marcaccio B, Crepaldi M, Postuma I, *et al*. Towards an adequate description of the dose-response relationship in BNCT of glioblastoma multiforme. *Med Phys*. 2025;52(4):2606–2617.
doi: 10.1002/mp.17693
7. Álvarez-Rodríguez P, Méndez-Malagón C, Porras-Quesada M, *et al*. Comparison of the Biological Response of a Head and Neck Carcinoma and a Glioblastoma Cell Line Under Neutron Irradiation with BPA Administration. *Biology*. 2025;14(9):1252.
doi: 10.3390/biology14091252
8. Postuma I, González S, Herrera MS, *et al*. A Novel Approach to Design and Evaluate BNCT Neutron Beams Combining Physical, Radiobiological, and Dosimetric Figures of Merit. *Biology*. 2021;10(3):174. Published 2021 Feb 26.
doi: 10.3390/biology10030174
9. Provenzano L, Koivunoro H, Postuma I, *et al*. The essential

- role of radiobiological figures of merit for the assessment and comparison of beam performances in boron neutron capture therapy. *Phys Med.* 2019;67:9-19.
doi: 10.1016/j.ejmp.2019.09.235
10. Bortolussi S, Postuma I, Protti N, *et al.* Understanding the potentiality of accelerator based-boron neutron capture therapy for osteosarcoma: dosimetry assessment based on the reported clinical experience. *Radiat Oncol.* 2017;12(1):130.
doi: 10.1186/s13014-017-0860-6
 11. Dattoli Viegas AM, Carando D, Koivunoro H, Joensuu H, González SJ. Predicting radiotoxic effects after BNCT for brain cancer using a novel dose calculation model. *Phys Med.* 2024;128:104840.
doi: 10.1016/j.ejmp.2024.104840
 12. Lea DE, Catchside DG. The mechanism of the induction by radiation of chromosome aberrations in *Tradescantia*. *J Genet.* 1942;44(2-3):216-245.
doi: 10.1007/bf02982830
 13. Morris GM, Coderre JA, Hopewell JW, *et al.* Response of the central nervous system to boron neutron capture irradiation: evaluation using rat spinal cord model. *Radiother Oncol.* 1994;32(3):249-255.
doi: 10.1016/0167-8140(94)90024-8
 14. Harjani RR, Gururajachar JM, Krishnaswamy U. Comprehensive assessment of Somnolence Syndrome in patients undergoing radiation to the brain. *Rep Pract Oncol Radiother.* 2016;21(6):560-566.
doi: 10.1016/j.rpor.2016.08.003
 15. Kankaanranta L, Seppälä T, Koivunoro H, *et al.* L-boronophenylalanine-mediated boron neutron capture therapy for malignant glioma progressing after external beam radiation therapy: a Phase I study. *Int J Radiat Oncol Biol Phys.* 2011;80(2):369-376.
doi: 10.1016/j.ijrobp.2010.02.031
 16. Woodford K. Somnolence syndrome after cranial irradiation: a literature review. *Radiographer.* 2007;54(3):30-33.
doi: 10.1002/j.2051-3909.2007.tb00074.x
 17. International Atomic Energy Agency. *Current status of neutron capture therapy*. IAEA; 2001. IAEA-TECDOC-1223. <https://www.iaea.org/publications/6168/current-status-of-neutron-capture-therapy>
 18. Niemierko A. Reporting and analyzing dose distributions: a concept of equivalent uniform dose. *Med Phys.* 1997;24(1):103-110.
doi: 10.1118/1.598063
 19. Sud S, Botticello T, Niemierko A, Daly J, Bussiere M, Shih HA. Dosimetric Comparison of Proton Versus Photon Radiosurgery for Treatment of Pituitary Adenoma. *Adv Radiat Oncol.* 2021;6(6):100806.
doi: 10.1016/j.adro.2021.100806
 20. Capoulat ME, Cartelli D, Baldo M, *et al.* Accelerator based-BNCT facilities worldwide and an update of the Buenos Aires project. *Appl Radiat Isot.* 2025;219:111723.
doi: 10.1016/j.apradiso.2025.111723
 21. Colonna N, Beaulieu L, Phair L, *et al.* Measurements of low-energy (d,n) reactions for BNCT. *Med Phys.* 1999;26(5):793-798.
doi: 10.1118/1.598599
 22. Goorley JT, Kiger WS, Zamenhof RG. Reference dosimetry calculations for neutron capture therapy with comparison of analytical and voxel models. *Med Phys.* 2002;29(2):145-156.
doi: 10.1118/1.1428758
 23. International Commission on Radiation Units and Measurements. *Photon, Electron, Proton and Neutron Interaction Data for Body Tissues*. ICRU Report 46. International Commission on Radiation Units and Measurements; 1992