

# MONTE CARLO ASSESSMENT OF BORON NEUTRON CAPTURE THERAPY FOR THE TREATMENT OF BREAST CANCER

by

**Daniel W. MUNDY and Tatjana JEVREMOVIC**

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For a large number of women who are diagnosed with breast cancer every year, the available treatment options are effective, though physically and mentally taxing. This work is a starting point of a study of the efficacy of boron neutron capture therapy as an alternative treatment for HER-2+ breast tumors. Using HER-2-specific monoclonal antibodies coupled with a boron-rich oligomeric phosphate diester, it may be possible to deliver sufficient amounts of  $^{10}\text{B}$  to a tumor of the breast to allow for selective cell destruction via irradiation by thermal neutrons. A comprehensive computational model (MCNP) for thermal neutron irradiation of the breast is described, as well as the results of calculations made using this model, in order to determine the optimum boron concentration within the tumor for an effective boron neutron capture therapy treatment, as compared with traditional X-ray radiotherapy. The results indicate that a boron concentration of 50-60  $\mu\text{g}$  per gram of tumor tissue is optimal when considering treatment times, dose distributions and skin sparing. However, these results are based upon best-guess assumptions that must be experimentally verified.

*Key words: boron neutron capture therapy, breast cancer, MCNP, oligomeric phosphate diester*

## INTRODUCTION

According to the U. S. National Cancer Institute, one of every eight women in the United States will develop breast cancer at some point during her lifetime. For the majority of those who are fortunate enough to be diagnosed at an early stage of the disease, the most common treatment option is a lumpectomy or mastectomy in which a portion or the entire breast is removed. The surgery is generally followed by chemotherapy and/or radiotherapy to ensure total eradication of the malignant cells [1]. Though this is considered routine treatment with a high success rate, the physical and mental stress suffered by the patient can be extreme. Moreover, approximately 30% of these tumors are resistant to the normal avenues of treatment, due to an over-expres-

sion of the gene related to the HER-2 (human epidermal growth factor receptor) protein which promotes malignant cell proliferation. The treatment of these HER-2-positive cancers is extremely difficult and recurrence is probable. For this reason, boron neutron capture therapy (BNCT) may provide an advantage over traditional therapy in the treatment of these types of cancers.

Boron neutron capture therapy is a binary cancer treatment designed to deliver a lethal dose to malignant cells while sparing the surrounding healthy tissue. Proposed in 1936, BNCT has been the topic of ongoing clinical investigation for the treatment of advanced glioma and melanoma since the early 1950's [2]. The theoretical concept of BNCT (illustrated in fig. 1) is to selectively deliver  $^{10}\text{B}$  to tumor cells, which are then irradiated with a beam of thermal (or epithermal) neutrons. The resulting reaction (eq. 1) releases an alpha particle and a lithium ion, both massively charged particles with high linear energy transfer (LET)



Of the 2.79 MeV released in the reaction, 1.47 MeV and 0.84 MeV are imparted to the alpha and the lithium ion, respectively, in the form

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Authors' address:

Purdue University, West Lafayette, IN 47907, USA

E-mail address of corresponding author:

dmundy@purdue.edu (D. W. Mundy)

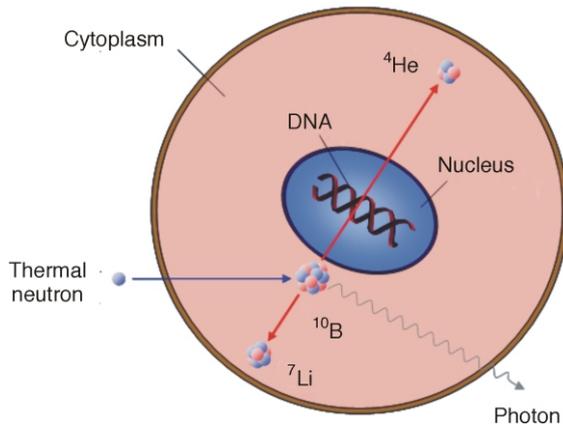


Figure 1. BNCT cell killing mechanism

of kinetic energy [3]. Due to the high-LET of these particles, this energy is deposited over a very short range of only 10 to 15  $\mu\text{m}$  combined (the approximate diameter of a human cell). This short range ensures that all energy released in the reaction is deposited within the cell in which the reaction takes place. On a larger scale, provided that the administered  $^{10}\text{B}$  is confined to the tumor volume, the majority of radiation-induced damage will occur within the tumor. The dose to the surrounding healthy tissue (due to thermal neutrons and a 0.48 MeV gamma that is emitted in 94% of the  $^{10}\text{B}(n, \gamma)^7\text{Li}$  reactions [2]) is greatly reduced in comparison to traditional X-ray radiotherapy. However, the effectiveness of this treatment is limited by the ability to selectively deliver boron to the tumor cells. For the treatment of glioma, it has been shown that a concentration of approximately 10-30  $\mu\text{g}$  of  $^{10}\text{B}$  per gram is required within the tumor, with a tumor to normal tissue concentration ratio of at least five to one [4]. It may be possible to achieve these conditions for the application of BNCT in the treatment of breast cancer using monoclonal antibodies (MABs) and oligomeric phosphate diesters (OPDs).

It is known that approximately 30% of all breast cancers exhibit an over-expression of the HER-2 gene [5]. These HER-2-positive tumors are statistically most resilient to treatment, due to the fact that amplification of the HER-2 gene causes increased numbers of HER-2 receptor sites at the cell surface which, in turn, cause increased proliferation of the tumor cells. However, it has been shown that treating HER-2-positive breast cancers with MAB (substances that bind to and therefore block specific receptors at the cell surface) causes a reduction in this uncontrolled growth [6]. The MAB specific to HER-2 receptor sites is known as Trastuzumab (available under the brand name Herceptin®) and is currently being used

as a treatment option for increasing the survival time of patients with HER-2-positive breast cancer. If combined with OPDs which are easily impregnated with  $^{10}\text{B}$  and easily linked to MABs, Trastuzumab may become an effective boron delivery agent for the treatment of breast cancer using BNCT. Unlike traditional boron delivery agents used for the treatment of glioma with BNCT, OPDs have been shown to exhibit highly selective uptake within the nucleus of a cell [7]. The proposed mechanism of action is that the combined MAB-OPD molecule binds to the HER-2 receptor sites at the surface of the tumor cells, where the boron-rich OPD is then taken up by the cell and accumulated in the nucleus. When exposed to a thermal neutron beam, neutrons are absorbed by the  $^{10}\text{B}$  and high energy, high-LET radiation is emitted. The result is irreparable damage to the cell DNA, eventually leading to apoptosis.

The focus of this work is the development of a computational model with which to study thermal neutron irradiation of the breast, as this is a novel application of BNCT. The primary parameters of interest in this study are the absorbed doses in both the tumor and the surrounding healthy tissue, as well as the concentration of boron within the tumor required to achieve the desired therapeutic results.

## METHODS

### Computational model

For the purpose of determining total dose rates due to thermal neutron irradiation of the breast, a complex computational model was developed using the Monte Carlo N-Particle (MCNP) transport code, version 5, developed at Los Alamos National Laboratory [8]. The model is based on a computational mammogram simulation developed by Bakić *et al.* [9], with slight simplifications made for ease of modeling and run-time reductions. The geometry, shown in fig. 2, consists of three regions: adipose tissue (AT), fibroglandular tissue (FGT), and malignant tumor tissue. As with a normal human female breast, the model is composed primarily of AT, with an FGT region extending parabolically inward from the area directly behind the nipple. The densities of AT and FGT are given as 0.93  $\text{g}/\text{cm}^3$  and 1.04  $\text{g}/\text{cm}^3$ , respectively [10], and the density of the tumor tissue is assumed to be 10% greater than that of the FGT (this assumption is likely low, and is therefore conservative for this study). The tumor was modeled as a series of cylindrical volumes (for computational ease) centered behind the nipple. The dimensions of the model are indicated in fig. 2, and the elemental composition of each tissue type given in tab. 1.

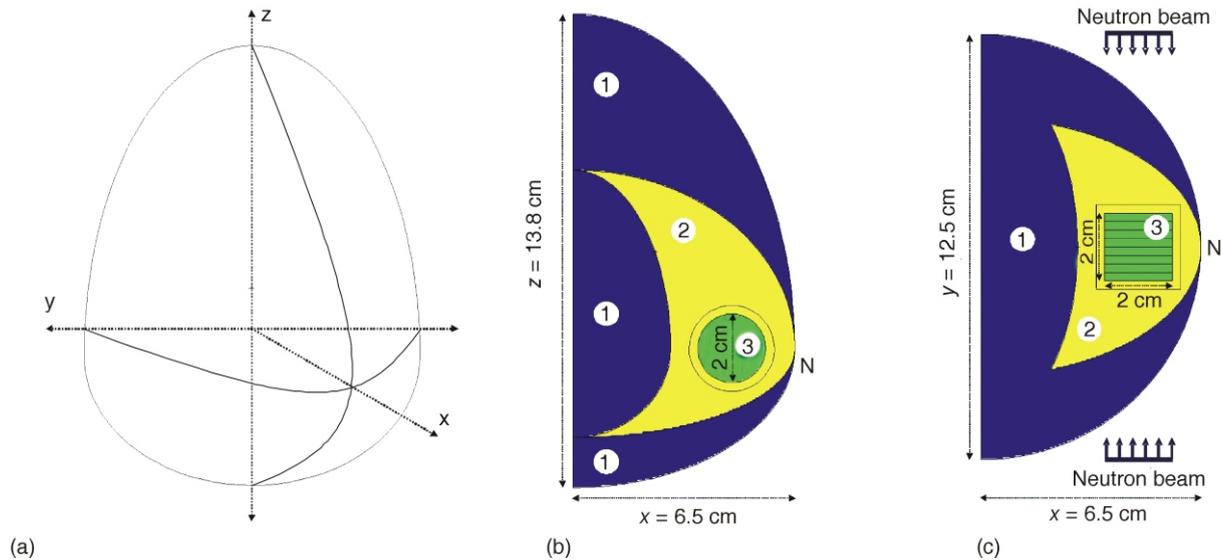


Figure 2. MCNP computational breast model. Shown here: a wire diagram of the model (a), cross-sectional view in the xz plane (b), and cross-sectional view in the xy plane (c). In each figure, each different material is indicated by a number (1 – AT; 2 – FGT; 3 – tumor tissue) and the location of the nipple is indicated by N

Table 1. Chemical compositions of tissue materials

Tissue type	Chemical composition [wt%]				
	H	C	N	O	P
AT [10]	11.2	61.9	1.7	25.1	1.0
FGT [10]	10.2	18.4	3.2	67.7	5.0
Tumor [10, 11]	9.9	26.9	4.5	56.9	1.8

Parallel opposed neutron beams were modeled as mono-energetic planar sources positioned as shown in fig. 2. The energy of the source neutrons was set at 0.0253 eV (purely thermal) and the diameter made equal to that of the tumor volume. The flux of each beam was set to  $5 \cdot 10^9 \text{ cm}^{-2}\text{s}^{-1}$ , which is an approximation of the maximum total neutron flux currently available for BNCT treatments [12]. It should be noted that the majority of BNCT treatment facilities utilize epithermal neutron beams, as they have been designed to treat brain tumors, for which the neutrons must penetrate the skull before reaching the tumor and therefore require a higher initial energy. The current study examines the application of purely thermal neutrons, as penetration of dense structures such as the skull is not required for the irradiation of breast tumors. Further studies will utilize epithermal spectra to determine whether these facilities offer an advantage in sparing healthy tissue.

### Radiobiology

If the results of this experiment are to be compared with those of traditional X-ray radiotherapy, considerations must be made for the relative biological effectiveness of the high-LET particles used in BNCT (neutrons, alphas, and heavy ions). In previ-

ous BNCT experiments, each dose component has been multiplied by a biological effectiveness factor which is determined experimentally for each particle and tumor type, as well as the boron delivery agent [3]. These factors are known as the relative biological effectiveness (RBE) value for neutrons and the compound biological effectiveness (CBE) value for products of the  $^{10}\text{B}(n, \gamma)^7\text{Li}$  reaction, and are described in units of Gray-Equivalent (Gy-Eq). They are determined by the dose of high-LET radiation required to produce a biological effect identical to a known X-ray (usually 250 kV at peak) dose. Because experiments using the proposed Trastuzumab-OPD compound have not yet taken place, average values of 2.7 and 3.8 [3] were used for the purposes of this model. It should be noted, however, that the RBE and CBE values are a function of boron distribution within the cell; *i. e.* higher if boron is localized in the cytoplasm rather than at the surface of the cell [3]. Since OPDs are known to localize within the *nucleus* of each cell [7], these parameters will likely have experimentally-determined values that are much greater than the assumed ones. This assumption is therefore conservative for the purposes of this study.

### RESULTS

This model was used to examine thermal neutron irradiation of the breast with varying concentrations of boron-10 in the tumor volume. Data obtained without the presence of boron provides the background dose rate due to thermal neutron interactions with the tissue. It has been shown that the minimum concentration of boron within the tumor

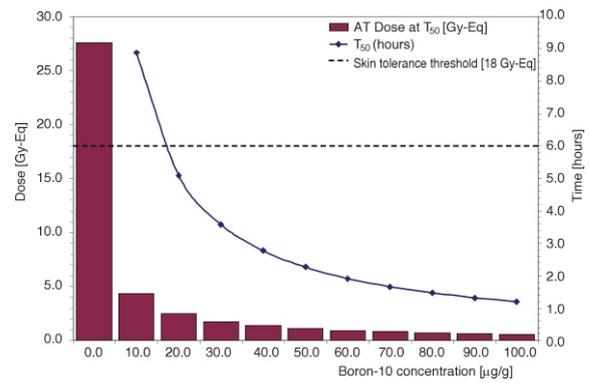
required for therapeutic gain in BNCT glioma treatments is approximately  $30 \text{ g }^{10}\text{B}$  per gram of tumor tissue [4]; therefore, boron concentrations ranging from 10 to  $100 \text{ g/g}$  were studied. The objective of these calculations is to determine an estimate of the boron concentration required to deliver a lethal dose to the entire tumor without exceeding the tolerance threshold of the skin.

For traditional X-ray radiotherapy treatment of breast tumors, the average dose prescription is approximately  $50 \text{ Gy}$  [13] and the tolerance limit of human skin for a single dose has been shown to be  $18 \text{ Gy}$ , at which point moist desquamation (peeling) occurs [3]. The objective of this study, thus, is to determine the boron concentration required to deliver  $50 \text{ Gy-Eq}$  to the tumor, while keeping the dose to the skin below  $18 \text{ Gy-Eq}$ . This was accomplished by determining the dose rate in both the tumor and the surrounding healthy tissue due to thermal neutrons alone, first. The tumor was then loaded with various concentrations of boron and the accompanying increase in dose rate within the tumor calculated. Finally, the minimum dose rate in the tumor (occurring at the center of the tumor volume) was used to determine the time required to reach a dose of  $50 \text{ Gy-Eq}$  ( $T_{50}$ ). This ensures that all portions of the tumor receive *at least* the average prescribed dose. The determined irradiation time was then used to calculate the maximum dose to the healthy tissue, including the skin (AT Dose at  $T_{50}$ ). The results are shown in fig. 3. It must be noted that these calculations assume that no boron is present within the healthy tissue, which is not a valid assumption when using previously developed boron delivery agents, such as BPA or BSH. However, experiments with OPDs indicate that a large concentration of the molecules remain in the nucleus up to and past 24 hours after the uptake [7]. This should provide ample time for excess carrier molecules to exit the bloodstream almost entirely. Further experimentation is required to verify this assumption.

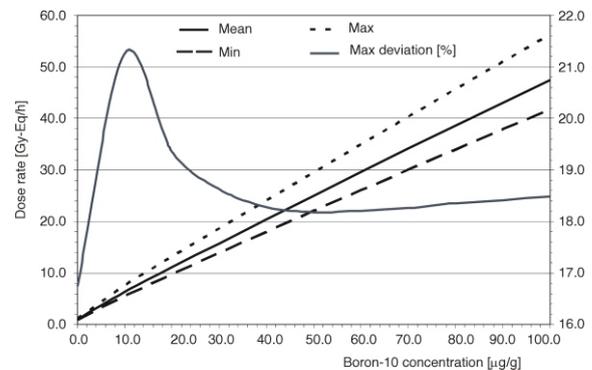
In addition to the data discussed above, the distribution of the dose within the tumor is of interest, too. The data plotted in fig. 3 represents the maximum dose to healthy tissue corresponding to the time required to obtain a minimum dose of  $50 \text{ Gy-Eq}$  in the tumor volume. However, as it is desirable to deliver an equal dose to all parts of the tumor, the deviation from the mean dose as a function of its position in the tumor must be examined. This data is presented in fig. 4.

## DISCUSSION AND CONCLUSION

As stated previously, the objective of this study was to determine the tumor boron concentration required to deliver a lethal dose to a breast tumor



**Figure 3.** Maximum dose to skin at  $T_{50}$  as a function of tumor boron concentration. The solid line indicates the irradiation time required to obtain a minimum dose of  $50 \text{ Gy-Eq}$  in the tumor volume ( $T_{50}$ ) and the dashed line indicates the skin tolerance threshold of  $18 \text{ Gy-Eq}$ . Associated computational errors are less than 1% and are not discernable at this scale



**Figure 4.** Dose rate variation within the tumor volume as a function of tumor boron concentration. The dark solid line indicates the mean dose rate, while the dotted and dashed lines indicate the maximum and minimum dose rates, respectively. The light solid line indicates the maximum deviation from the mean dose. Associated computational errors are less than 1% and are not discernable at this scale

(comparable to that normally prescribed in traditional radiotherapy) using BNCT while keeping the dose to the healthy tissue below the skin tolerance level. While the results of this experiment presented in fig. 3 indicate that a boron concentration as low as  $10 \text{ g}$  of  $^{10}\text{B}$  per gram of tissue in the tumor could satisfy this objective, other factors must be taken into account, too. For instance, though a concentration of only  $10 \text{ g/g}$  may be sufficient, a concentration of  $100 \text{ g/g}$  reduces the irradiation time by a factor of approximately 9.0, which corresponds to a factor of an approximately 5.0 reduction in the dose to the healthy tissue. The obvious advantages to a higher boron concentration are a reduced dose to the healthy tissue, as well as an improvement in the comfort of the patient as a result of shorter irradiation times.

Additionally, as indicated by the data presented in fig. 4, the variation of the dose rate across the tumor volume varies significantly with boron concentration and must be considered when determining the optimum boron concentration. As the goal of any radiation treatment is to deliver an equal dose to all portions of a target volume, extreme boron concentrations (low or high) may not be advantageous, as these points are relative maxima in the deviation from the mean dose rate.

From both figs. 3 and 4, it appears that the optimum tumor boron concentration for the treatment of breast cancer via BNCT is between 50 and 60 g of  $^{10}\text{B}$  per gram of tumor tissue. This range provides a minimum deviation from the mean dose rate throughout the tumor volume and requires a workable irradiation period of approximately two hours. However, it must be reiterated that these results are based upon the following assumptions: (1) that the tumor density is 10% greater than that of the surrounding tissue, (2) that the RBE and CBE values for the Trastuzumab-OPD compound in a breast tumor are similar to those of BPA and BSH in brain tumors and melanoma, and (3) that the concentration of boron in healthy tissue is negligible. The results of this study are subject to experimental verification of these assumptions.

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Данијел В. МУНДИ, Татјана ЈЕВРЕМОВИЋ

### МОНТЕ КАРЛО АНАЛИЗА БОРОНСКЕ ТЕРАПИЈЕ РАКА ДОЈКЕ

Велики број жена оболелих од рака дојке у САД сваке године подлеже прописаном ефективном протоколу лечења који није ни мало једноставан и лак. Овај рад фокусиран је на анализу ефикасности боронске неутронске терапије као алтернативног приступа лечењу рака дојке који показује пролиферацију HER-2 протеина. Користећи HER-2 специфична моноклонална антитела везана за олигомерске молекуле богате боронским једињењима могуће је депоновати захтевану количину  $^{10}\text{B}$  у тумору дојке што би омогућило селективно уништење ћелија тумора по озрачивању термалним неутронима. Овај рад приказује детаљан модел боронске терапије у примени рака дојке на бази Монте Карло програма MCNP5. Резултати прорачуна су анализирани у поређењу са конвенцијалном терапијом X-зрачењем у погледу поља зрачења и депоноване дозе зрачења у тумору и здравом ткиву. Анализе показују да би оптимална концентрација  $^{10}\text{B}$  у тумору била између 50 и 60  $\mu\text{g}$  по граму ткива тумора посматрајући време озрачивања пацијента, просторну расподелу дозе као и вредност дозе коју прими кожа у току третмана. Одређене претпоставке коришћене у овом раду предмет су експеримената планираних да се обаве у САД и Јапану.

*Кључне речи: боронска неутронска терапија, рак дојке, MCNP, OPD*

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