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Dose Analysis of Brain Cancer Therapy with Boron Neutron Capture Therapy (BNCT) using PHITS V.3.33

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ABSTRACT

One type of brain cancer, glioblastoma (GBM), attacks glial cells and belongs to the glioma category. While MRI imaging is mainly used to create geometric images of brain cancers, Boron Neutron Capture Therapy (BNCT) was known for destroying cancer cells in a single treatment or cleavage session. On the other hand, the PHITS (Particle and Heavy Ion Transport Code System) code can help in radiotherapy plans using model simulation. This study aims to analyze the absorbed dose by each organ and determine the shortest irradiation time for each beam direction. This study used 90° (Left-Lateral) and 0° (postero-anterior) angular orientations in combination with varied boron concentrations of 40 µg/g, 80 µg/g, 100 µg/g, and 150 µg/g. The results showed that this study's 90° angle orientation (L-LAT) with a boron concentration of 150 µg/g was optimal. The shortest exposure time of 33.18 minutes resulted in the absorbed doses of 1.77 Gy for the skin, which is below the dose tolerance limit of 2 Gy; the spinal organ absorbs 5.43 Gy, below the tolerance limit of 14 Gy; and the brain receives 2.38 Gy, below the tolerance limit of 3 Gy.

1. INTRODUCTION

Cancer is a serious disease characterized by abnormal cell growth. In brain cancer, cancer cells multiply uncontrollably and spread to surrounding tissues. According to the World Health Organization (WHO), brain cancer is the most common type of cancer worldwide, with 321,731 reported cases. In addition, brain cancer ranks 12th with 248,500 deaths and a mortality rate of 77.24%. According to GLOBOCAN, there are 5,738 cases of brain cancer in Indonesia, ranking 18th with a total of 5,259 deaths, which puts brain cancer at 13th with a mortality rate of 91.65%. [1]

A glioma is a type of brain cancer that originates in glial cells, which support the function of the central nervous system. These cancers can develop in the brain or spinal cord, which then spread to nearby tissues. Glioblastoma (GBM) is the main type of brain cancer that originates from astrocytes, a type of glial cell [2]

GBM falls under the category of grade IV glioma, which is characterized by extremely aggressive cell growth. Research suggests that genetic factors, abnormalities in the brain or nervous system, and previous radiation exposure may play a role in its development [3].

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As the cancer grows larger, the intracranial pressure in the brain increases. This can lead to seizures, confusion, memory problems, and muscle weakness.

Radiotherapy is considered the most effective method of treating brain cancer. Boron Neutron Capture Therapy (BNCT), which uses the isotope ^{10}B to capture neutrons and destroy cancer cells, is considered an innovative and effective option for difficult-to-treat cancer. This method employs neutrons, which have a higher relative biological effectiveness (RBE) than X-rays because BNCT serves as a target-based cancer therapy that directly destroys cancer cells. BNCT excels in terms of selectivity, minimal damage to healthy tissue, and is effective for aggressive or radioresistant tumors, but requires a specialized infrastructure and is not yet widely available.

Meanwhile, X-ray is more practical and accessible, suitable for various types of cancer, but has a higher risk of damage to surrounding healthy tissue and requires multiple therapy sessions. BNCT is also highly selective in GBM cases since damage only occurs to cells accumulating target boron. Healthy tissues that do not contain boron are not directly affected. In contrast, X-ray is less selective as the radiation affects all the tissues it passes through, both tumor and healthy tissues.

In general, BNCT works by destroying cancer cells with alpha particles. As ^{10}B is absorbed by cancer cells which has a significant thermal neutron cross-section of 3.838 barns, then thermal neutrons were captured by boron. This reaction produces ^{7}Li and alpha particles (helium), as described by equation (1) [4].

$$ {}^{10}_{5}B + {}^{1}_{0}n \rightarrow [{}^{11}_{5}B]^{*} \rightarrow \begin{cases} {}^{4}_{2}He + {}^{7}_{3}Li + 2.79\ MeV\ (6.1\%) \\ {}^{4}_{2}He + [{}^{7}_{3}Li]^{*} + 2.31\ MeV\ (93.9\%) \\ {}^{7}_{3}Li + \gamma(0.48\ MeV)\ (1) \end{cases} \quad (1) $$

These alpha particles have a high linear energy transfer (LET) and a shorter range than photons, allowing them to deliver targeted radiation doses to specific areas. BNCT is also preferred because it can eliminate cancer cells in a single treatment session or separate sessions [5]

BNCT is recognized as a complementary cancer therapy; boron-containing drugs are first administered to cancer cells. The ^{10}B concentration within cancer tissue is higher than in healthy tissue, hence, when irradiated with neutrons, it triggers the ^{10}B (n,α) ^{7}Li reaction. The emitted α-particles and lithium nuclei release high energy over very short distances, which are comparable to the size of normal cells. Consequently, neutron irradiation effectively destroys cancer cells [6].

The probability of interaction between a neutron and a nucleus can be calculated by comparing the number of interactions that occur to the number of neutrons that reach the nucleus through the thickness (t). The neutron microscopic cross-section describes how much the probability for each interaction is, denoted by σ with units of barn (b), where 1 barn is equivalent to 10^{-28} m². The cross-section value is affected by neutron energy and the target isotope's properties. The number of particles produced by a target material with the area of A and material with an atomic density of N when exposed to neutron flux Φ can be seen in equation 2 [7]

$$ R = \Phi \times \{N \times A \times t\} \times \sigma \quad (2) $$

The reaction rate of neutrons was linear to the neutron flux. As neutrons move through a medium, they are scattered in different directions, changing energy or velocity distributions [7]

Currently, BNCT are developed in several countries around the world. For neutron sources, accelerator-based BNCT (AB-BNCT) has been developed in Russia, Japan, the UK, Italy, Israel, and Argentina. Iran, Finland, China, and Italy developed reactor-based BNCT basic research. While the neutron source based on 30 MeV cyclotron was developed in Japan [8]

PHITS version 3.33 is a Monte Carlo-based software designed for solving the transport of heavy particles and ions. Developed by the Japan Atomic Energy Agency (JAEA), PHITS is a versatile code written in FORTRAN. PHITS can be used for modeling nearly all types of radiation particles, including neutrons, electrons, photons, ions, positrons, and hadrons, across a wide range of energies (from $10^{(-4)}$ eV to the order of TeV) [9]. PHITS is known for its ability to interact with various types of particles, including those associated with BNCT, and can transfer energy of up to 30 MeV [10]. One significant advantage of PHITS version 3.33 is its ability to calculate the absorbed dose for brain cancer accurately. This capability is crucial for enhancing treatment efficacy and minimizing adverse effects on surrounding healthy brain tissue [11].

This study aims to evaluate the radiation dose received by each organ and identify the minimum irradiation time for different irradiation directions in BNCT-based brain cancer therapy using PHITS simulation. This in-depth analysis not only supports the development of brain cancer-specific BNCT techniques but also opens the possibility for other types of cancer that can be modeled with similar approaches [12].

2. RESEARCH METHODS

2.1. MRI Cancer Imaging

Magnetic Resonance Imaging (MRI) is a medical procedure that uses strong magnetic fields and radio waves to create detailed images of the body's organs and tissues.

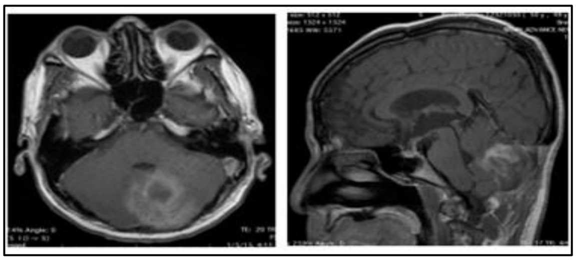

Figure 1. The MRI results for brain cancer show the image on the left displaying the position of the cancer from above, while the image on the right shows the position of the cancer from the left side [13].

MRI employs large magnets to create a powerful magnetic field, causing protons, particularly those from hydrogen atoms in the body, to align with that field. Hydrogen contains magnetically active protons. Once the protons are aligned, MRI transmits radio waves at a frequency of about 10^4 Hz. Radio waves change the alignment of the protons in the area being imaged, causing them to absorb energy and move to a higher energy state. When the radio waves are turned off, the protons return to a lower energy state and release energy. This process is called relaxation. During this time, the sensors in the MRI record the emitted energy while the receiver coils capture the signals. The computer then processes these signals using complex algorithms to create 2D or 3D images. Tissue containing much water (H_2O) appears as white areas on the MRI images, while areas with less water appear black. MRI images of the brain offer detailed information about the anatomy and structure of the nervous system. This widely used non-invasive imaging technique offers excellent soft tissue contrast and produces multispectral images [14].

2.2. PHITS Modeling

PHITS version 3.33 was used to model particle interactions and heavy ion transport in detail [10]. Simulations were done with a notebook PC with an Intel Core Ultra 5 125H Processor 16GB, 512GB WINDOWS 11, Notepad++ 7.8.8 was used to develop geometry in PHITS, while Ghostscript and Ghostview were used for plotting simulation output. Standard Microsoft Office was used for preparing data for input and post-processing the output.

The first step was a literature review, followed by the review and creation of input code for the program. Once the input code was completed, the next step was to create the phantom geometry, as shown in Figure 2. After that, an input file was created, and the simulation could be done with 100,000,000 neutron histories to achieve a statistical error below 10%. Once the results were calculated, the final step was to analyze them.

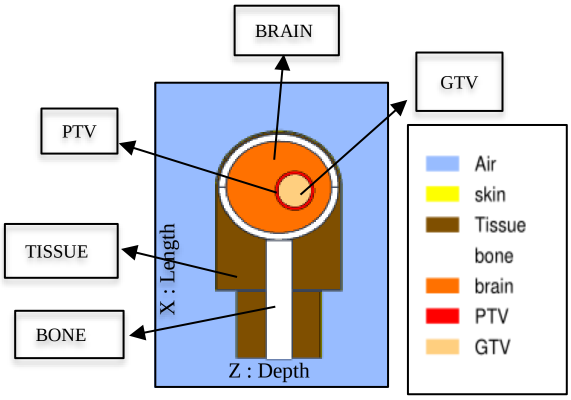

Figure 2. 2-Dimension geometry results

The phantom model used refers to the ORNL-MIRD phantom with a size equivalent to an adult male. The cancer is assumed to be spherical and consists of three target areas: gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV). The depth of the cancer is estimated to be approximately 1.5 to 2 cm from the skin surface. The dimensions of the GTV, CTV, and PTV for the cancer are 5 cm x 4.2 cm x 4 cm. [15]. Organ at risk (OAR) are highly sensitive to radiation and can be easily damaged when exposed to radiation [16]. The composition of the phantom organs being modeled can be found in the ICRP, i.e. composition of the brain can be seen in Table 1 [17].

Table 1. Brain material elements

H	C	N	O	Na	P	S	Cl	K	Dens
10.7	14.3	2.3	71.3	0.2	0.4	0.2	0.3	0.3	1.041

Phantom geometry can also be created by calculating or using formulas found in mathematical phantoms. The OAR used in this study includes skin, bone, soft tissue, and brain. Based on the results of the geometry model created with the ORNL phantom for adult males, the geometry shown in Figure 2 produces a two-dimensional shape. The direction of the neutron beam and the distribution of the beam used in this study are the 90° angle or L-LAT (Left lateral) and the 0° angle or PA (Postero-Anterior).

2.3. Neutron Source

The neutron source directed into the body originates from a collimator. The collimator utilized in this study is known as the Beam Shaping Assembly (BSA) with whose primary function is to slow down fast neutrons [18]. The shape of the BSA collimator can be seen in Figure 3

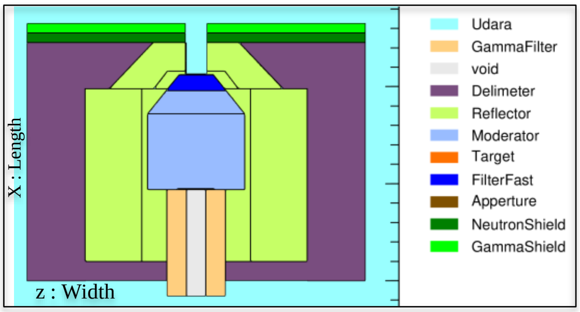

Fig 3. BSA Collimator Geometry Results

The values obtained from the BSA must conform to IAEA parameter standards. The axial epithermal neutron flux in the recommended design is 1.03×10^{-9} n/cm^2, while, as shown in Table 3, almost all IAEA or BSA BNCT design parameters have been met [19].

Table 3. Neutron flux characteristics

Parameters	IAEA Standard	Optimization
Epithermal Neutron Flux	$>1.0\times10^{9}$	1.37×10^{9}
Fast neutron dose rate/epithermal neutron flux	$< 2.0\times10^{-12}$	6.85×10^{-23}
Gamma dose rate/epithermal neutron flux	$< 2.0\times10^{-12}$	1.5×10^{-22}
Ratio of thermal and epithermal fluxes	< 0.05	1.68×10^{-2}
The Ratio of neutron current and neutron flux	> 0.7	7.39×10^{-1}

2.4. Dosimetry

BNCT is based on nuclear reactions and involves calculating four dose components: boron dose, neutron dose, proton dose, and gamma dose. The dose rates of these four components can be obtained from the output tally results. PHITS software was used to calculate the total dose rate, irradiation time, and equivalent dose, which were then calculated with Microsoft Excel.

a. Calculation of total dose rate

The total dose rate can be determined by adding the dose rates of each component and then multiplying them by the radiation quality factor of the radiation source. The quality factor values for different types of ionizing radiation in BNCT are provided in Table 2. The total dose rate values can be calculated using the formula in Equation 3 [20].

$$Dt = D\gamma.W\gamma + Dn.Wn + Dp.Wp + Db.Wb \quad (3)$$

Table 2. Radiation Quality Factors

Source	Radiation Quality Factor	Symbol
Boron	3.8 (cancer) 1.3 (Healthy network)	*Wb*
Proton	3.2	*Wp*
Neutron	3.2	*Wn*
Gamma	1	*Wγ*

b. Irradiation Time

To destroy cancer cells, BNCT requires an estimated therapy duration. The irradiation time (t) can be calculated based on the minimum dose required to achieve the GTV dose. In this study, the minimum dose necessary to kill cancer cells is 60 Gy. [21]. The irradiation time for cancer treatment can be calculated using Equation 4, where the total dose corresponds to the total dose rate.

$$Irradiation\ time\ (s) = \frac{Dose\ Minimum\ (Gy)}{\dot{D}_{Total}\ (\frac{Gy}{s})} \quad (4)$$

c. Eequivalent Dose

The equivalent dose can be calculated for both healthy tissue and cancerous tissue. This dose is used to assess the damage experienced by healthy tissue surrounding the cancer, and it can be calculated using Equation 5.

$$D_{Eq}OAR(Gy) = (E\dot{D}OAR\,\frac{Gy}{s}) \text{ x Irradiation time (s)} \quad (5)$$

3. RESULT AND DISCUSSION

In BNCT therapy, epithermal neutrons coming out of the collimator turn into thermal neutrons after entering the body. When these thermal neutrons interact with the cancer cell injected with ^{10}B, the ^{10}B turns into metastable ^{11}B. The interaction between thermal neutrons and boron produces various reactions. ^{7}Li and ^{4}He (α particles) with two different probabilities. In the first scenario, with a probability of 6.1%, ^{7}Li with an energy of 2.79 MeV is produced. The second scenario has a higher probability of 93.9% with the system emitting gamma rays with an energy of 0.48 MeV.

BNCT serves as a target-based cancer therapy that directly destroys cancer cells due to the selective absorption of ^{10}B by cancer cells and its high cross-section of 3.838 barn to thermal neutrons, minimizing the dose received by healthy tissues [5]. In BNCT, the interaction between neutrons and boron results in damage to brain cancer cells while minimizing damage to healthy tissue. This occurs because boron selectively accumulates in cancer cells, and the alpha particles and lithium ions produced have a short range. However, the effectiveness of this therapy is highly dependent on accurate boron distribution, the quality of the neutron source, and proper dose planning to minimize potential damage to healthy tissue.

BNCT is also particularly suitable for invasive and radioresistant tumors such as glioblastoma multiforme (GBM), melanoma, and head-neck cancers that are difficult to treat with conventional therapies. The results of the distribution of irradiation energy released by BSA against cancer can be seen in Figures 4 and 5.

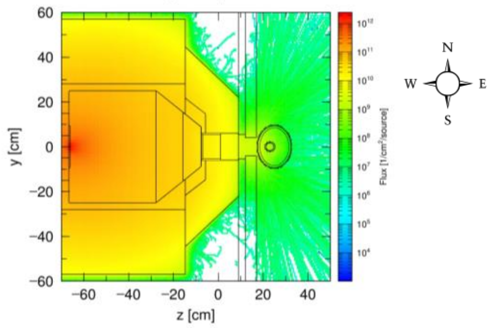

Figure 4. Results of irradiance distribution in the 90° direction, the image shows the patient facing north, with the BSA collimator positioned on the left side of the patient's head (L-LAT)

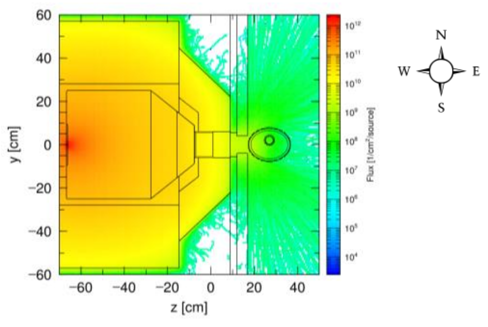

Figure 5. Results of 0° The image shows the patient facing east, with the BSA collimator positioned behind the patient's head.or (PA) directional irradiance distribution

This 90° irradiation angle is called L-LAT for Left Lateral, with the irradiation direction originating from the left side of the patient's body and is directed to the right. The Left Lateral is usually used to target cancer or areas that need treatment in the middle or right part of the body. The distance from the neutron source to the skin tissue is 1 cm, while the distance to the cancer tissue (GTV) is 5.2 cm.

This 0° angle of illumination is called P-PA, which stands for Postero-Anterior, for the irradiation direction from back to front. In the context of radiotherapy, this means that the radiation source is placed behind the patient, and the radiation is directed towards the front of the patient's body. This technique is often used to target cancer or areas located in the anterior part of the body or the middle, while minimizing radiation exposure to vital organs that may be located closer to the radiation source if a different approach is used. The distance from the neutron source to the skin tissue is only 1 cm, while the distance to the cancer tissue (GTV) is 8.2 cm.

In this study, the cancer was localized at the lower left rear of the head. L-LAT is more suitable for tumors located on these sides as it can reduce exposure to central structures, but requires extra protection of lateral tissues, while PA is more suitable for tumors located on the posterior or midline, although it requires special treatment to protect the cerebellum and brainstem. Therefore, irradiation from the 90° direction, commonly called L-LAT, is more effective because the neutron source's distance to the cancer tissue is closer, so radiation from the L-LAT direction directly targets the cancer tissue. The goal is to ensure that the dose received by the surrounding tissue (Organs At Risk - OAR) is minimized.

The characteristics of neutron flux received by each organ, as shown in Table 2, are adequate. The output graph of neutron flux corresponding to depth can be observed in Figure 6.

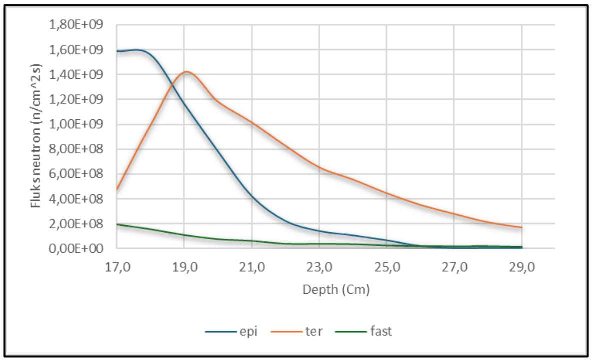

Figure 6. Graph of neutron flux per depth

Figure 6 shows that the epithermal neutron flux value at a depth of 0 cm decreases immediately when compared to the thermal neutron flux. This drop is due to the proton beam, which generates a neutron beam when it is fired at the beryllium (^{9}Be) plate, resulting in a specific reaction:

$$[^{9}_{4}Be] + [^{1}_{1}p]\ (30\ MeV) \rightarrow [^{10}_{5}B]^{*} \qquad (6)$$

Fast neutrons will enter the BSA collimator. Neutrons with energy greater than 10 keV will be slowed down by the BSA into thermal neutrons (less than 0.5 eV) or epithermal neutrons (0.5 eV to 10 keV).

Figure 6 shows that at a depth of 0-2 cm, thermal neutrons increase due to the presence of cancerous tissue at this depth. This is because the concentration of ^{10}B in cancer tissue will produce higher energy than other healthy tissues; after all, when thermal neutrons interact with boron, a reaction produces particles that damage cancer cells. In addition, the epithermal flux also shows a decrease, which is caused by absorption interactions in the tissue by hydrogen and nitrogen atoms.

The flux value obtained will affect the dose rate value received by OAR, as shown in Figure 7, which shows the dose rate distribution of boron, neutron, proton, and nitrogen atoms. Gamma on irradiation L-LAT, and Figure 8 shows the boron, neutron, proton, and gamma dose rate distributions under PA irradiation.

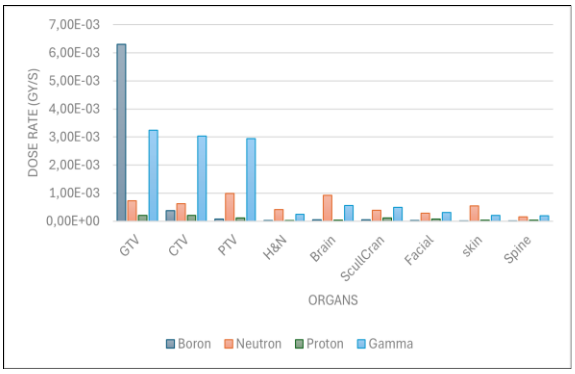

Figure 7. Distribution of dose rates for boron, neutrons, protons, and gamma radiation at a concentration of 150 µg/g in the L-LAT irradiation direction.

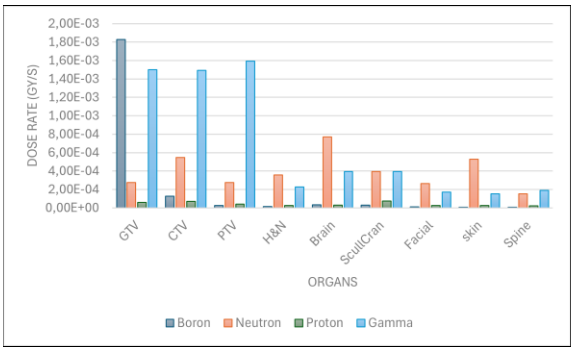

Figure 8. Distribution of dose rates for boron, neutrons, protons, and gamma radiation at a concentration of 150 µg/g in the PA irradiation direction.

The boron dose rate results are higher than the other dose rates. This suggests that the boron concentration in cancerous tissue influences the dose rate. Additionally, the GTV value for the boron dose is significantly higher than the boron dose rates found in other tissues.

The total dose rate determines the irradiation time. The ratio of boron concentration in cancerous tissue to that in healthy tissue is 10:1. Healthy tissue will only receive 0.3% of the total boron concentration injected into the body, ensuring that the cancerous tissue receives a significantly higher concentration than the healthy tissue. The results of the total dose rate graphs in Figs 9 and 10 show that the OAR has different values in the L-LAT and PA directions.

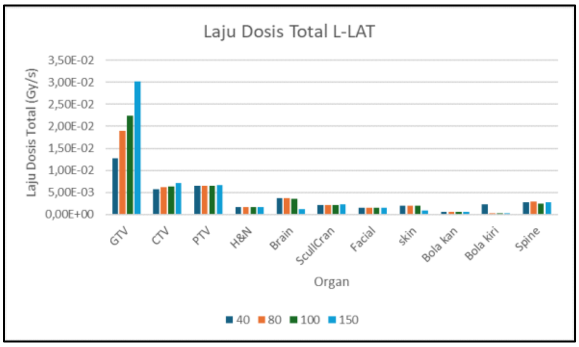

Figure 9. Total OAR Dose Rate in the L-LAT direction

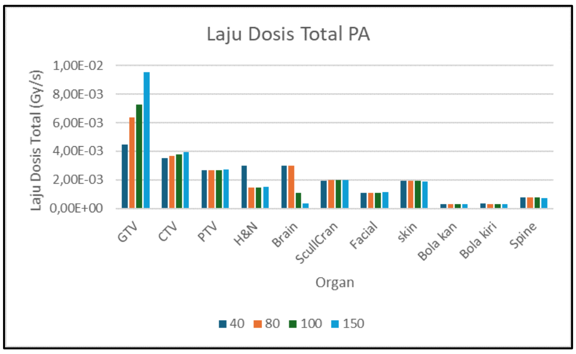

Figure 10. Total OAR Dose Rate in the PA direction

BNCT Therapy Time takes an average of 1 hour while the correlation of boron concentration and total treatment duration can be seen in Table 4, with the value obtained calculated using Equation 3.

Table 4. Relationship between irradiation time and boron concentration in each irradiation.

Concentration	L-LAT	PA
	Irradiation time (minutes)	
40 μ/g	78.43	224.09
80 μ/g	62.48	157.52
100 μ/g	44.49	137.52
150 μ/g	33.18	105.07

The relationship between irradiation time and boron concentration can also be seen in the graph shown in Figure 11. The shortest time occurs in the L-LAT direction with a boron concentration of 150 µg/g, at 33.18 minutes, or less than 1 hour. The longest time occurs in the PA direction with a boron concentration of 40 µg/g, at 224.09 minutes, or equivalent to 3 hours and 73 minutes.

Neutron irradiation affects not only the cancerous tissue, but also the surrounding healthy tissue. This is due to the ability of healthy tissue to absorb Boron, albeit in small amounts, about 1%. Since the irradiation time is most effective in the L-LAT irradiation direction with a boron concentration of 150 µg, the resulting absorbed dose value is presented in Table 5. [22]

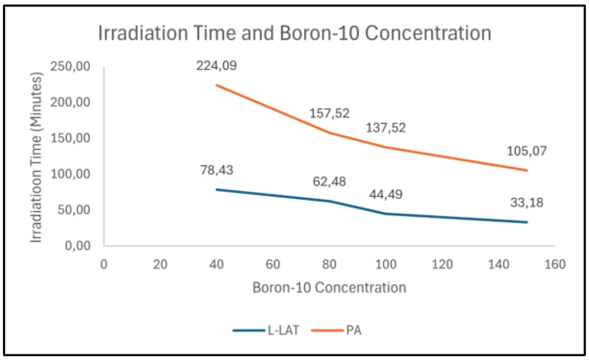

Figure 11. Graph of the relationship between irradiation time and boron concentration in each irradiation.

Table 5. OAR dose and irradiation direction

OAR	Irradiation Technique	L-LAT	PA
	Dose Tolerance(Gy)	Absorbed Dose (Gy)	
Skin	2	1.77	11.70
Spine	14	5.43	4.38
Brain	3	2.38	2.27

Table 5 shows that the L-LAT technique requires shorter irradiation times and lower absorbed doses to the organs at risk. Specifically, the absorbed dose to the skin in the L-LAT direction is 1.77 Gy, close to the reference dose tolerance limit. In contrast, the absorbed dose in the PA direction is 11.70 Gy, which greatly exceeded the dose tolerance limit [23]. Deterministic effects on skin organs include Erythema (redness) in the dose range of 2-3 Gy, dry peeling at 3-8 Gy, wet peeling (festering) at 12-20 Gy, and tissue death if the dose is more than 20 Gy [23].

For the spinal cord, the absorbed dose with L-LAT of 5.43 Gy is close to the established dose tolerance limit of 14 Gy, while in the PA direction, the absorbed dose of 4.38 Gy is close to the limit. If the spinal cord dose exceeds the tolerance limit of 14 Gy, it may result in paralysis or even death [24] In the brain, the absorbed dose is measured in the L-LAT direction, reaching 2.38 Gy, well below the established limit of 3 Gy. In the PA direction, the absorbed dose is 2.27 Gy, also significantly under the tolerance limit. If the absorbed dose to the brain exceeds the tolerance limit, it could lead to symptomatic necrosis disease. [25]

Thus, the L-LAT technique was safer from the calculated result in this study, as PA is more suitable for tumors located posteriorly or midline, but requires special care to protect the cerebellum and brainstem, while L-LAT is more suitable for tumors on the sides of the brain, reducing exposure to central structures, although it requires extra protection for lateral tissues. As a result, the dose absorbed by each organ and the irradiation time are safer in the L-LAT direction. These findings were consistent with the recent study by Bilalodin et al. (2023) in the Journal of Physics, which analyzed the dose rate and irradiation duration of BNCT therapy in head cancer using PHITS simulation.

The maximum dose rate in the GTV area was 6.37 x 10^{-2} Gy/s with a boron concentration of 80 μg/g tissue, so the effective therapy duration was calculated to be 13.08 minutes. The relevance of this research lies in the PHITS simulation technique, with the difference in the cancer object studied. The results of this study are fully in accordance with the case study being considered, since a higher boron concentration needs shorter irradiation time. In addition, the analysis results show that the dose absorbed by healthy organs remains below the set tolerance limits, thus supporting the safety of this method in further applications.

4. CONCLUSION

Based on the results of this study, it can be concluded that the L-LAT (Left-Lateral) irradiation direction provides the most optimal performance in therapy delivery. With an irradiation angle of 90° and a boron concentration of 150 μg/g, the optimal irradiation time was determined to be 33.18 minutes. This configuration allows radiation to be focused on the tumor area in the left hemisphere of the brain while effectively reducing the dose received by healthy tissues on the opposite side, such as the right optic nerve and the brainstem. All absorbed doses in critical organs remained below the established tolerance limits, indicating that this direction is both safe and effective for use in BNCT therapy.

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AUTHOR'S CONTRIBUTION

The primary contributors to this article are **Alfiyah Sulistiawati**, Ideas; formulation or evolution of overarching research goals and aims, Development or design of methodology; creation of models, Programming, software development; designing computer programs; implementation of the computer PHITS code and supporting algorithms; testing of existing PHITS code components. **Subur Pramono**, Verification, whether as a part of the activity or separate, of the overall replication/ reproducibility of results/experiments and other research outputs. **Beta Nur Pratiwi**, Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data. **Gede Sutresna Wijaya**, Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools. **Isman Mulyadi Triatmoko**, Management activities to annotate (produce metadata), scrub data and maintain research data (including software PHITS code, where it is necessary for interpreting the data itself) for initial use and later reuse. **Yohannes Sardjono**, conducting research and the investigation process, specifically performing the experiments, or data/evidence collection. **Nunung Nuraeni**, Preparation, creation, and/or presentation of the published work, specifically writing the initial draft (including substantive translation). **Heru Prasetio**, Preparation, creation, and/or presentation of the published work by those from the original research group, specifically critical review, commentary, or revision – including pre-or postpublication stages. **Nur Rahmah Hidayati**, Preparation, creation, and/or presentation of the published work, specifically visualization data presentation. **Syarifatul Ulya**, Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team, cancer therapy, and **Zuhdi Ismail**, Management and coordination responsibility for the research activity planning and execution. All authors have reviewed and approved the final version of the manuscript.

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