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Dose Analysis of Esophageal Cancer Therapy with Boron Neutron Capture Therapy (BNCT) Using PHITS Version 3.33

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A B S T R A C T

Based on statistics from the World Health Organization (WHO) in 2022, esophageal cancer ranks 7th out of 15 types of cancer that cause the highest number of deaths in the world. Boron Neutron Capture Therapy (BNCT) is a proven therapeutic method for treating esophageal cancer, as it delivers high doses of radiation selectively to cancer cells while minimizing damage to healthy tissue. This research was carried out to determine the dose absorbed by esophageal cancer, as well as to determine the optimum boron concentration, irradiation time, and irradiation direction to kill cancer utilizing the Particle and Heavy Ion Transport Code System (PHITS) software version 3.33. PHITS simulates BNCT therapy on esophageal cancer with the Monte Carlo method. According to the existing literature, no studies have explored esophageal cancer treatment using BNCT therapy in conjunction with Monte Carlo method simulation with PHITS. The results showed that the irradiation direction of 0° with a boron concentration of 150 $\mu g/g$ produced a lower absorbed dose and was more efficient in irradiation time. The shortest irradiation time obtained was 31 minutes with a dose absorbed by the esophagus of 2.77 Gy, while the dose absorbed by the skin was 1.78 Gy.

1. INTRODUCTION

World Health Organization (WHO) data for 2022 [1], noted that the number of global esophageal cancer cases reached 511.054, with 445.391 deaths recorded. The percentage of esophageal cancer cases reached 2.6%, while the rate of fatalities was 4,6%. Regarding gender distribution, the rate of cases in men is 7.6%, while in women it is 2.6%. Globally, new cases of esophageal cancer rank 11th in number of cases and 7th in number of deaths. In Indonesia, there were 408.661 new cases in general, with a total of 242.988 deaths recorded. In esophageal cancer, There were 1.382 new cases and 1.330 deaths.

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The percentage of esophageal cancer cases in Indonesia was 1.382 new cases and 1.330 deaths. The percentage of esophageal cancer cases in Indonesia is 0.34%, while the rate of deaths reaches a is 0.34%, while the rate number of deaths reaches 0.55%. In Indonesia, new cases of esophageal cancer rank 25th in number of cases and 21st in number of deaths [1].

The esophagus is a muscular, tube-shaped organ that passes food from the throat to the stomach [2]. Esophageal cancer is a type of cancerous growth affecting the digestive system tract caused by factors such as advanced age, malnutrition, and difficulty swallowing food. This condition tends to be more common in older men [3]. Esophageal cancer can be treated with various methods of treatment, such as surgery, chemotherapy, radiotherapy, targeted therapy, preventive measures, and early diagnosis.

Surgery is the main method of esophageal cancer treatment, especially in the early stages, to remove cancerous tissue. Chemotherapy and radiotherapy are often used together to shrink the tumor before or after surgery, or as a standalone treatment to eliminate residual cancer cells post-surgery [4].

A frequently used radio diagnostic method for esophageal cancer is a PET/CT scan. The advantages of PET/CT scan are its ability to improve the accuracy of diagnosis at an early stage, detect abnormal cell metabolic activity at a small stage, and identify small metastases in lymph nodes and tumor recurrence outside the body [5].

According to Locher (1936), BNCT is a form of cancer therapy that utilizes the capacity of boron-10 for neutron absorption. When boron-10 encounters a neutron, a nuclear process produces high-energy particles capable of killing cancer cells [6]. Boron-10 exhibits a significant reaction cross section of 3837 barns (1 barn = $1 \times 10^{-24} cm^2$) against thermal neutron capture, making it effective as a cancer treatment through the $^{10}\mathrm{B}(\mathrm{n},\alpha)^{7}\mathrm{Li}$ process, which generates alpha and lithium particles [7].

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

Equation (1) is the reaction of ^{10}B with thermal neutrons [8].

Boron taken into the body tends to accumulate more in the tumor cells. Thus, when tumor cells are exposed to neutrons, they can be specifically destroyed [9]. The success of BNCT treatment is based on two main elements: the concentration of boron within the tumor cells and the sufficient amounts of thermal neutrons needed to trigger the reaction [10]. One advantage of BNCT is its capacity to selectively and effectively deliver boron to cancerous cells. The use of a carrier agent improves the distribution of boron throughout the body. Two commonly utilized carrier agents in BNCT are boronophenylalanine (BPA) and borocaptate sodium (BSH) [11]. The main function of the boron carrier agent is to deliver boron to tumor cells in patients [9],[12].

BNCT is currently being developed in several countries worldwide. Russia, Japan, the UK, Italy, Israel, and Argentina are developing accelerator-based BNCT (AB-BNCT) for neutron sources. Iran, Finland, China, and Italy are conducting basic research on reactor-based BNCT, while Japan is developing a 30 MeV cyclotron-based neutron source [13]. BNCT technology currently utilizes accelerators for neutron sources, replacing reactor-based neutron sources, which are considered less efficient and require more space [10]. A radio Frequency (RF) cyclotron is also considered a neutron source in BNCT therapy [14].

PHITS is a software designed to calculate the interactions between radiation of particles coming from various sources with matter using the Monte Carlo method. Developed by Japanese and European researchers, the program is known for its ability to simulate multiple types of radiation with a wide energy spectrum, including particles and electrons [15]. Compared to several similar programs such as FLUKA, GEANT4, and MCNP, PHITS lies in the shortest simulation time and uses less material at the same level of phantom complexity [16],[17]. The simulation includes all types of radionuclides and particle emissions such as α, β, γ, positron, and electron (Auger). PHITS can estimate the average dose for cancer cells and their surrounding areas. The program can also reproduce source particles for every organ geometry utilizing the multisource capability of PHITS [18],[19].

PHITS can be used to perform detailed Monte Carlo simulations for calculating radiation dose parameters, which are crucial for radiology areas, particularly in BNCT applications. This is important because physical measurements of the dose inside the tumor are often difficult. With PHITS, researchers can calculate the thermal neutron flux and gamma dose rate within the tumor to understand the dose distribution and effectiveness of therapy. In addition, PHITS also enables characterization of the radiation field, especially under validation against experimental data, thus giving more confidence to the dose calculations required for therapy [20].

2. METHODOLOGY

BNCT is a cancer treatment method that utilizes neutrons to selectively target and damage cancer cells. Patients are given boron compounds that collect on cancer cells and then irradiated with neutrons. When the boron absorbs the neutrons, a reaction occurs that produces radiation that can destroy the tumor without damaging the surrounding healthy tissue. PHITS simulation is used to optimize BNCT by modeling the movement of neutrons through the body as well as their interaction with boron and biological tissues. PHITS can calculate the radiation dose received by the tumor, healthy tissues, and their distribution. This study could provide more precise and effective treatment planning.

2.1. Phantom Geometry Modeling

To model the radiation transport process within the human body, various materials have been utilized to create phantoms that resemble body and organ tissues [21]. The type of phantom geometry modeling used by the researcher is the Oak Ridge National Library (ORNL), which represents an adult male [22]. Each organ is prepared based on the guidelines contained in ICRP 145 [23].

There is no specific standard for determining the CTV-PTV (Clinical Target Volume - Planning Target Volume) margin since it needs to be tailored to the individual patient's physical condition as well as the precision of the hospital's equipment. Typically, CTV is established by enlarging the GTV (Gross Tumor Volume) margin by approximately 2-4 mm, while the PTV is defined by extending the CTV margin in all three dimensions by about 5-10 mm [24]. As a reference for the simulation results, the axial slice PET/CT data of a 61-year-old male patient who was diagnosed with primary squamous cell carcinoma located in the distal part of the esophagus, classified as stage II esophageal cancer (T3N0M0), is illustrated in Figure 1 [25].

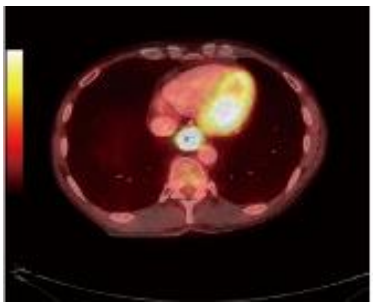

Figure 1. PET/CT of an esophageal cancer patient [25].

In the study, the GTV has a radius of 0.915 cm, the CTV has a radius of 1.415 cm, and the PTV has a radius of 1.615 cm. The visualization of a mathematical phantom generated by ORNL in a 2-dimensional geometry of the esophageal cancer phantom is illustrated in Figure 2. Organs at risk of radiation exposure when treating esophageal cancer are the lungs, heart, spinal cord, esophagus, stomach, liver, and kidneys [26]. However, the radiation will pass through the skin first before hitting these organs.

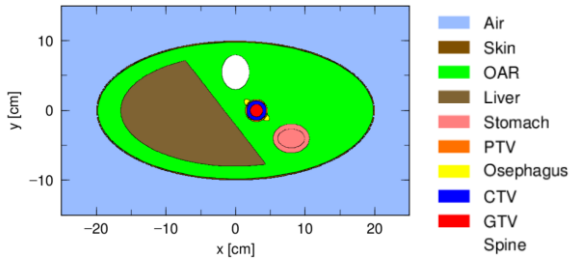

Figure 2. Geometry of esophageal cancer phantom and surrounding organs.

2.2. Neutron Source

BNCT depends on a neutron source to generate thermal neutrons that interact with boron-10 accumulated in the tumor. The HM-30 cyclotron is used as a neutron source, which, according to Kyoto University, can produce proton beams with high energy of 30 MeV, essential for BNCT study [27]. In addition, this cyclotron can produce a proton beam with an intensity of 1 mA [28]. The BSA (Beam Shaping Assembly) is a device used to shape the neutron beam from the cyclotron output. The BSA geometry being modeled for this study is illustrated in Figure 3.

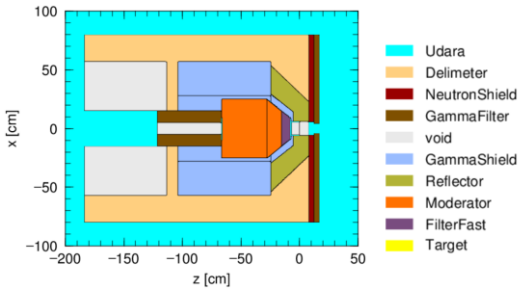

Figure 3. BSA optimization geometry.

The standard set by the IAEA requires that the BSA generate a neutron beam with a proper epithermal to thermal neutron flux ratio [29]. The results of BSA optimization with a gamma shielding thickness of 5 cm can be seen in Table 1

Table 1. BSA optimization results in a gamma shielding thickness of 5 cm.

Parameter	Notation	IAEA Recommendation	Optimization Results
Epithermal neutron flux	$\phi_{epi}(n / cm^2 s)$	$> 1.09 \times 10^9$	1.37×10^9
Fast neutron dose rate/epithermal neutron flux	$\frac{D_{fast}}{\phi_{epi}}(Gy.cm^2/n)$	$< 2.0 \times 10^{-13}$	9.37×10^{-14}
Gamma dose rate/thermal neutron flux	$\frac{D_{\gamma}}{\phi_{epi}}(Gy.cm^2/n)$	$< 2.0 \times 10^{-13}$	1.54×10^{-13}
Ratio of thermal to epithermal fluxes	ϕ_{th}/ϕ_{epi}	< 0.05	0.016

Ratio of neutron current and neutron flux	J/ϕ_{epi}	> 0.7	0.73

Table 1 shows that each criterion for the used optimized BSA model has fulfilled the IAEA recommendation. Flux optimization on BSA was performed without the use of the ORNL phantom while dose rate optimization on BSA was performed using a water phantom. The water phantom was used to represent the human body because 75% of the human body consists of water

2.3. Dosimetry

In BNCT, there are four primary types of dose components: boron, proton, neutron, and gamma doses [30]. Each dose component is multiplied by its constitute radiation weighting factor to get the total dose rate. Equation (2) shows the overall radiation exposure rate in BNCT [31].

$$\dot{D}_{total} = w_b \times \dot{D}_b + w_p \times \dot{D}_p + w_n \times \dot{D}_n + w_\gamma \times \dot{D}_\gamma \quad (2)$$

$\dot{D}_{total}$ represents the cumulative dose rate. In contrast, w_b, w_p, w_n, and w_γ represent the radiation quality factors for boron, protons, neutron scattering, and gamma radiation quality factors, respectively.

The BNCT dose requires an estimate of the therapy time to destroy cancer cells. The dose that can kill cancer cells in esophageal cancer ranges from 20-50.4 Gy [32]. The duration of irradiation was then calculated by dividing the minimum dose required to eliminate the cancer by the overall dose rate, as expressed in equation (3) [33].

$$\text{time irradiation (s)} = \frac{\text{dose minimum damage to cancer (Gy)}}{\text{total dose rate (Gy/s)}} \quad (3)$$

The absorbed dose refers to the total radiation energy absorbed by the tissue in a given time [34]. The amount of radiation absorbed by each organ is possible after the irradiation time is set. The dose can be analyzed to ensure that the total dose does not surpass the dose limit received by the organ at risk (OAR) or healthy organs. Equation (4) is used to calculate the absorbed dose [33].

$$Dose\ (Gy) = dose\ rate\ (Gy/s) \times irradiation\ time\ (s) \quad (4)$$

3. RESULTS AND DISCUSSION

The research outcomes include the BSA optimization, BNCT dose rate, irradiation time, and the amount of radiation exposure experienced by the organs that are at risk modeled by phantom organs along with cancer cells. This study uses variations in the direction of irradiation and variations in boron concentration to accumulate within the cancer cells. The variations in the irradiation direction are angle $0^{\circ}, 145^{\circ}$, and 180° seen in Figure 4-6, while the variations in boron concentration are $120 \mu g/g$ and $150\ \mu g/g$.

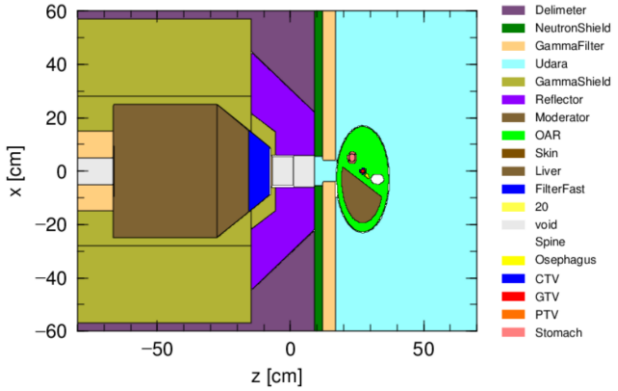

Figure 4. Visualization of irradiation angle of 0°.

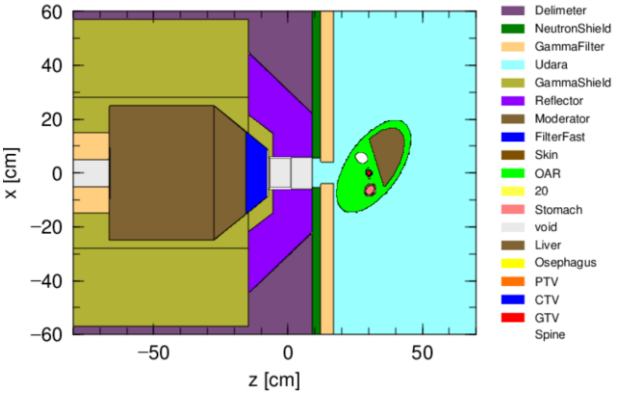

Figure 5. Visualization of irradiation angle of 145°.

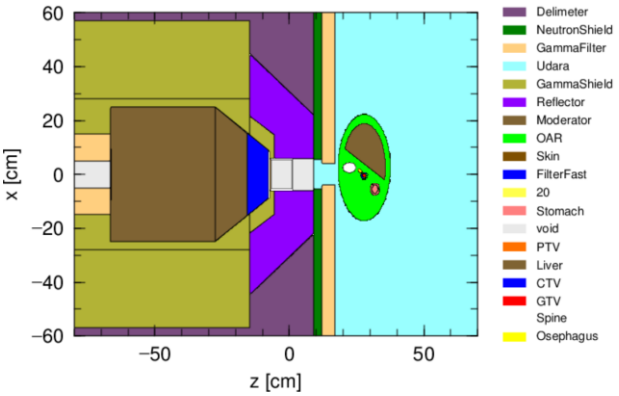

Figure 6. Visualization of irradiation angle of 180°.

The 0° angle direction is the direction of radiation from the front to the back of the patient's body or AP (Anterior-Posterior). The 145° angle direction is the direction of radiation from the left side of the patient's body or LLAT (Left Lateral). While the 180° angle direction is the direction of radiation from the back to the front of the patient's

body or PA (Posterior-Anterior). A comparison of the three irradiation directions is to determine the position of irradiation that affects esophageal cancer.

The distance of BSA head to cancer tissue from these simulated neutron beam directions varies. The target tissue (GTV) and the neutron organ source are 9.1 cm away in 0° angle direction, 12 cm away in the 145° angle direction, and 9.8 cm away in the 180° angle direction. Therefore, radiation from the 0° angle direction is more effective than the other angle directions since the cancer tissue is closer to the neutron source, increasing the neutron flux reaching the cancer tissue.

The purpose of flux distribution in the ORNL phantom is to visualize the neutron flux distribution of thermal, epithermal, and fast energy. Fast neutrons generated from proton collisions with Beryllium are mediated by BSA, producing epithermal neutrons. Epithermal neutrons that pass through the body will interact with various atomic materials in the body such as H, C, N, O, Na, P, S, Cl, and others. This reduces the epithermal neutron, while the thermal neutron increases as reported by Bilalodin (2023) [35].

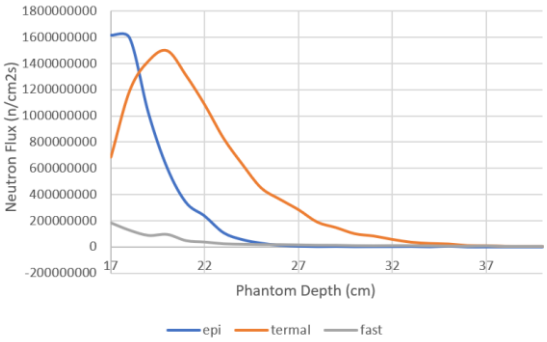

Figure 7. Neutron flux distribution graph per depth at neutron beam angle 0°.

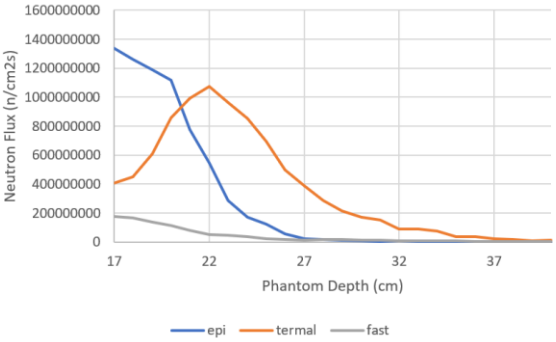

Figure 8. Neutron flux distribution graph per depth at neutron beam angle 145°.

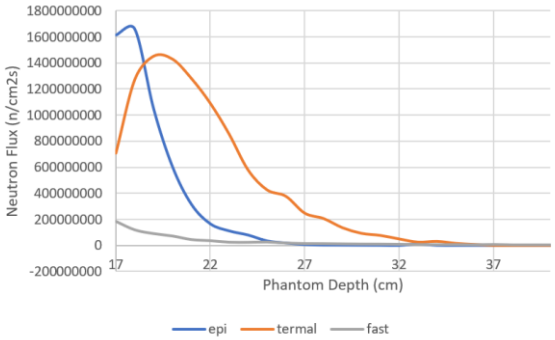

Figure 9. Neutron flux distribution graph per depth at angle 180°.

Figures 7-9 show the neutron flux distribution graphs for all three neutron beam directions. It can be seen that the pattern of the three curves decreases as the depth increases. This phenomenon occurs because neutrons undergo moderation, which is the process of slowing down or decreasing neutron energy due to interactions with cell tissue materials, especially light elements such as hydrogen and nitrogen. The simulation results show that the epithermal neutron flux curve is below the thermal neutron flux curve, which indicates that the amount of epithermal flux is smaller. This decrease is due to the energy loss of epithermal neutrons penetrating the tissue. Meanwhile, the thermal neutron flux curve increases at a depth of about 2-3 cm from the skin surface due to the additional thermal flux from neutron moderation.

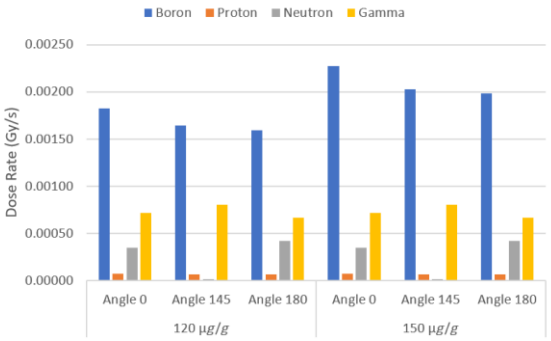

Figure 10. Dose rate component on GTV.

Figure 10 shows that the most dominant dose rate is the boron dose. The boron dose rate results from the thermal neutron capture reaction to the boron absorbed by cancer tissue. The higher the boron concentration, the greater the thermal neutron capture, so the boron dose rate increases with higher boron concentration. Since the atomic composition of hydrogen and nitrogen does not change, the other three dose rates do not increase significantly.

The total dose rate received by cancer tissue and organs at risk (OAR) for each B-10 concentration and irradiation direction can be seen in Figure 11-12. The total dose rate value in GTV increases as the B-

10 concentration increases. This increase is due to the significant contribution of the boron dose rate in the calculation of the total dose rate, especially in cancerous tissue. Meanwhile, in OAR, there is instability in the total dose rate value against the variation of B-10 concentration, because the B-10 concentration of OAR is very low, so the contribution of the boron dose rate does not affect the total dose rate. The total dose rate value of cancer tissue at a concentration of 150 $\mu g/g$ is greater than at a concentration of 120 $\mu g/g$ for all variations in irradiation direction.

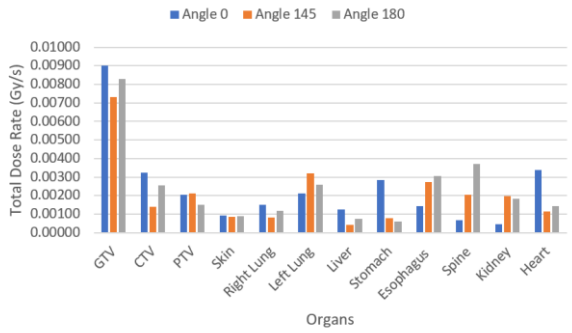

Figure 11. Relationship between total dose rate and OAR at a concentration 120 $\mu g/g$.

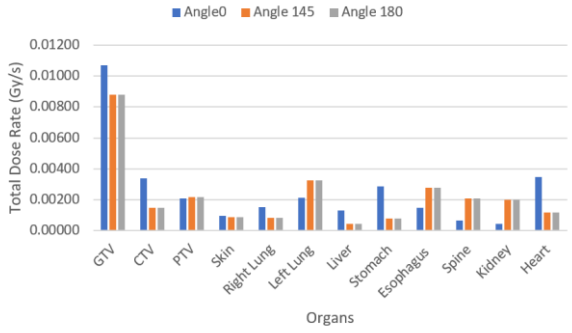

Figure 12. Relationship between total dose rate and OAR at a concentration of 150 $\mu g/g$.

After obtaining the total dose rate, the irradiation time is then calculated to justify the length of irradiation time. The calculated irradiation time for each irradiation direction and boron concentration can be seen in Figure 13. BNCT therapy requires a relatively long irradiation time, up to about 1 hour, as it is performed in one session (single fraction) [36]. According to Figure 11, the resulting time is below 1 hour, but the shortest time occurs at an angle of 0° with a concentration of 150 $\mu g/g$ for 31 minutes.

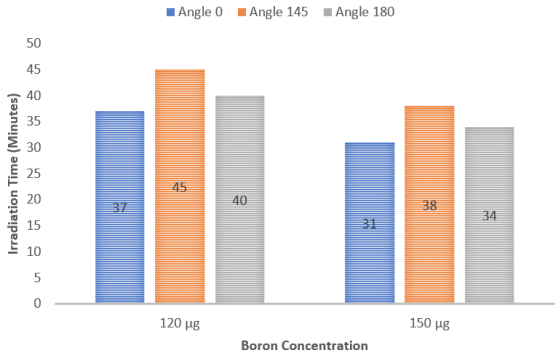

Figure 13. Relationship between neutron irradiation time and Boron concentration in each irradiation direction.

The dose rate value is inversely proportional to the irradiation time. The small dose of boron requires longer irradiation time, and vice versa. The dose received by each organ was calculated by multiplying the dose rate value by the irradiation time as mentioned in equation (4). The BNCT technique of cancer treatment uses a single dose of neutron radiation.

Figure 14-15 shows the doses absorbed by cancer tissues and organs at risk (OAR) with different boron concentrations. It is important to monitor the dose received by the OAR as it is quite high during therapy. It is anticipated that the dose received by OAR is below the dose threshold limit. For OAR, the skin and esophagus are used as indicators for damage during therapy. Table 2 compares the dose value and the dose limit for skin and esophagus.

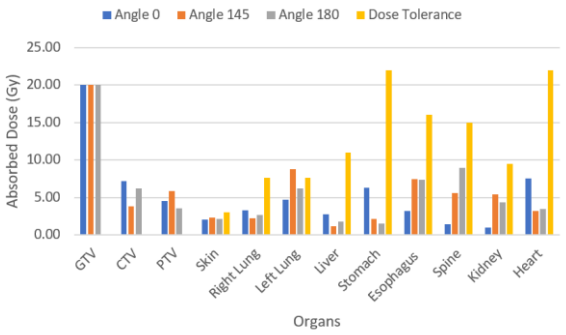

Figure 14. Relationship between absorbed dose and Organs at Risk (OAR) at a concentration of 120 $\mu g/g$.

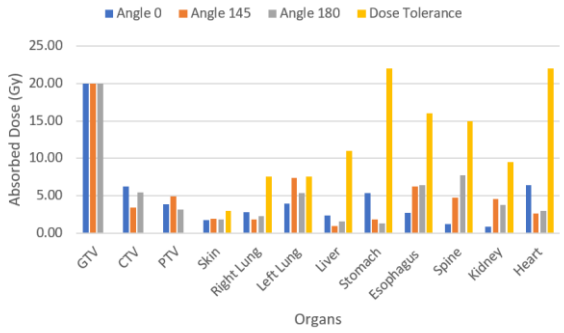

Figure 15. Relationship between absorbed dose and Organs at Risk (OAR) at a concentration of 150 $\mu g/g$.

The skin will experience the effect of erythema (redness) if it exceeds the dose tolerance limit of 3 Gy [37]. While the esophagus will experience stenosis or narrowing the dose exceeds the tolerance limit of 16 Gy [38].

Table 2. Dosage in OAR.

Boron Concentration	Irradiation Direction	OAR	Absorbed Dose (Gy)	Dose Tolerance (Gy)
120 µg	Angle 0°	Skin	2.10	3
		Esophagus	3.23	16
	Angle 145°	Skin	2.35	3
		Esophagus	7.46	16
	Angle 180°	Skin	2.15	3
		Esophagus	7.39	16
150 µg	Angle 0°	Skin	1.78	3
		Esophagus	2.77	16
	Angle 145°	Skin	1.97	3
		Esophagus	6.28	16
	Angle 180°	Skin	1.84	3
		Esophagus	6.39	16

At a concentration of 120 $\mu g/g$, the angle of 0° the dose absorbed in the skin is 2.10 Gy, and in the esophagus is 3.23 Gy. For an angle of 145° the absorbed dose on the skin is 2.35 Gy, and on the esophagus is 7.46 Gy. For an angle of 180°, the dose absorbed in the skin was 2.15 Gy, in the esophagus it was 7.39 Gy.

Whereas at a concentration of 150 $\mu g/g$, the dose absorbed in the skin is 1.78 Gy, and in the esophagus is 2.77 Gy for angle of 0°. For angle 145° the absorbed dose on the skin is 1.97 Gy, and on the esophagus is 6.28 Gy. For an angle of 180° the absorbed dose to the skin was 1.84 Gy, and to the esophagus was 6.39 Gy.

4. CONCLUSION

The simulation of esophageal cancer therapy with BNCT using the PHITS program concludes that the irradiation direction of the neutron beam angle of 0° with a concentration of 150 $\mu g/g$ is more effective for minimizing damage to OAR (Organ at Risk) compared to angles 145°, and 180°, or 120 $\mu g/g$ concentrations. All doses are below the threshold limit. At an angle of 0° with a concentration of 150 $\mu g/g$, the shortest irradiation time obtained is 31 minutes with a dose absorbed by the esophagus of 2.77 Gy, while the dose absorbed by the skin is 1.78 Gy.

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AUTHOR CONTRIBUTIONS

Salis Raidalliani: Ideas; formulation or evolution of overarching research goals and aim, 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; **Yohannes Sardjono:** Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection; **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; **Nunung Nuraini:** 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; **Zuhdi Ismail:** Management and coordination responsibility for the research activity planning and execution.

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