Journal of Holistic Medical Technologies
Vol.1 No.2 (2025) 81 – 91
Available online at https://journal.innoscientia.org/index.php/jhmt

Dose analysis of Boron Neutron Capture Therapy (BNCT) in brain cancer based on Cyclotron using PHITS application simulation

Muhammad Ghozali[1]* and Heni Sumarti[1]
[1]Department of Physics, Faculty of Science and Technology, Universitas Islam Negeri Walisongo Semarang, Indonesia
*Corresponding author's e-mail: mghozali100@gmail.com

ABSTRACT

One of the cancers is brain cancer, the most dangerous of which is Glioblastoma Multiforme (GBM). The research conducted aims to determine the effect of boron concentration on the boron dose rate, irradiation time and absorbed dose. Current cancer treatment still provides deterministic effects (tissue reactions) of radiation to patients and long therapy times. Therefore, researchers conducted research on Boron Neutron Capture Therapy (BNCT) in the treatment of cancer patients that is more selective in destroying cancer cells and is safe because it does not damage healthy tissues around it and the therapy requires a short time. The type of research conducted is quantitative experimental research. The research method with simulation uses the Particle and Heavy Ions Transport code System (PHITS) application on therapy process of Boron Neutron Capture Therapy (BNCT) for brain cancer patients type of Glioma grade 4 called Glioblastoma Multiforme. Patient modeling is based on the Oak Ridge National Laboratory-Medical Internal Radiation Dose (ORNL-MIRD) phantom in adult men who have a brain cancer diameter of 4 cm at a depth of 7 cm with a neutron source from a 30 MeV Cyclotron. The boron concentration used has 3 variations, as follows 20 µg/g, 40 µg/g and 60 µg/g of cancer tissue. Based on the results of the study at a boron concentration of 60 µg/g in the Gross Total Volume (GTV) organ or the center of cancer cells with a dose rate value of 11,160 x 10-2 Gy/s, thus accelerating the irradiation time within a period of 4 minutes 48 seconds and the absorbed dose increases by 30 Gy. Thus, it can be concluded that the higher the boron concentration, the faster the boron dose rate value, the greater the absorbed dose and the faster the irradiation time when carrying out brain cancer therapy.

Keywords:
Brain Cancer; Boron Dose; Cyclotron, BNCT, PHITS.

Introduction

Nowadays there are several deadly diseases, one of which is cancer. Cancer is a very dangerous disease caused by uncontrolled cell mass growth and the spread of abnormal cells to other tissues. Based on data from the International Agency for Research on Cancer (IARC) in 2020, 10 million people died from cancer (IARC, 2020). According to data from the Global Cancer Observatory-Global Burden of Cancer (GLOBOCAN) in 2020 there were 19.3 million new cases, 49.3% of which were in Asia, 22.8% in Europe, 20.9% in America, 5.7% in Africa and 1.3% in Oceania (Globocan, 2020). According to data from the Ministry of Health of the Republic of Indonesia (Kemenkes RI) in 2020, the incidence of cancer in Indonesia is in first place in Southeast Asia reaching 396,914 people, followed by Thailand in second place with 187,677 people and Vietnam in third place with 181,333 people (Pulungan & Hardy, 2020).

One of the cancers is brain cancer. Brain cancer is a collection of several malignant tumors in the form of a mass of cells that develop and grow rapidly and uncontrollably in the brain. The types of brain cancer are Glioblastoma Multiforme, Anaplastic Oligodendroglioma, Anaplastic Ependymoma. Brain cancer begins when brain cells grow abnormally. Symptoms that appear are headaches,

numbness, nausea, vomiting and seizures (Perkins et al., 2016). Brain cancer in Indonesia ranks 15th out of many cancers. In Indonesia, new cases of brain cancer in 2016 were 15,103 people with a death rate of 8,286 people, then in 2018 there were 16,499 people with a death rate of 9,418 people, then in 2020 there were 17,895 people with a death rate of 10,550 people, in this case every year the cases of brain cancer in Indonesia are increasing (Sung et al., 2021).

Most types of brain cancer suffered are Glioblastoma Multiforme (GBM), it turns out to be the most dangerous. GBM is included in the grade 4 glioma group based on the World Health Organization (WHO) classification, which is the brain cancer most often experienced by adults and also has a very poor prognosis (Komori, 2017). GBM is a malignant neuroepithelial tumor (cancer) originating from the supporting glial cells of the central nervous system. Histologically, GBM has been identified by increased levels of anaplasia (changes in cells in a tissue, both in size, structure and composition) and aggressiveness (Taylor et al., 2019).

All types of cancer, especially brain cancer, can be cured with various methods ranging from surgery, radiotherapy and chemotherapy (Navarro-Olvera et al., 2017). However, in reality the development of these methods, they are still not optimal, for example surgery is only for cancer that has enlarged and developed, but cannot cure cancer in the metastatic condition (early stage), then radiotherapy can kill cancer, but can damage cells around the cancer, then chemotherapy can cause side effects, such as hair loss and diarrhea (Miller et al., 2019).

Therefore, it is necessary to develop a new method, namely Boron Neutron Capture Therapy (BNCT). BNCT was discovered in 1936 by G. L. Locher, a scientist at The Franklin Institute in Philadelphia, Pennsylvania, United States. The BNCT method uses a neutron source that is indirectly transferred to the location of cancer cells. The principle of this BNCT has the ability of non-radioactive isotopes, namely boron-10 which can capture thermal neutrons, resulting in a nuclear reaction. From this reaction, two high Linear Energy Transfer (LET) particles are produced, including alpha particles (α) and lithium (7Li). The energy of the alpha particles is 150 keV/μm and 175 keV/μm at the lithium nuclei with a very limited tissue penetration distance has diameter size of one single cell (4 μm to 10 μm) (Matsuya et al., 2020).

The large energy produced causes cancer cells containing boron-10 is given to cancer patients, through intravenous injection (method of administering drugs through blood vessels) so that causes cancer cells will be destroyed and will not damage the surrounding healthy tissue. In the research conducted, BNCT uses thermal neutrons. The use of neutrons for cancer cells on the skin surface and located at a depth of 8 cm to 10 cm from the skin surface (Mokhtari et al., 2020).

The existence of technology that has developed now, research on the importance of boron concentration on the boron dose rate by increasing the boron concentration. The use of boron is chosen because boron absorbs neutrons, causing thermal neutron interactions and boron-10 (Monti Hughes & Hu, 2023). Boron is chosen because as a boronated compound as an ideal target agent because boron has properties including, high selectivity, low toxicity, can dissolve in water well because most of the cells are water and high absorption by cancer cells. The impact if the amount of boron is inserted into the patient's body will affect the boron dose rate (Laudensia et al., 2020).

Previous research used a thermal neutron radiation source from the Thermal Column Collimator model of the Kartini Research Reactor with a power of 100 kW with program simulation of Monte Carlo N-Particle eXtended (MCNPX) version 2.6.0. Variations in boron concentration include 20 μg/g, 25 μg/g, 30 μg/g and 35 μg/g of cancer tissue (Mahmud, 2017). Based on this, the study was conducted using the application simulation of PHITS version 3.33 with a neutron radiation source from a 30 MeV Cyclotron and variations in boron concentrations used were 20 μg/g, 40 μg/g and 60 μg/g of cancer tissue. Previous research was also used a neutron source from the Kartini Research Reactor with a power of 100 kW and a boron concentration of 30 μg/g of cancer tissue with program simulation of MCNPX (Handayani et al., 2023). Based on this, the research was conducted using the application simulation of PHITS version 3.33. The neutron radiation source from the Cyclotron has an energy of 30 MeV. There are 3 variations of boron concentration used, as follows 20 μg/g, 40 μg/g and 60 μg/g of cancer tissue. Based on the background and theory of the research, the formulation of the problem is the effect of boron concentration on the boron dose rate value, irradiation time and absorbed dose. The research aims to determine the effect of boron concentration on the boron dose rate value, irradiation time and absorbed dose. This requires research and development of BNCT in Indonesia to reduce the incidence

of cancer sufferers, especially the type of brain cancer is Glioblastoma Multiforme (Mokhtari et al., 2020).

Methods

Type of Research
The research used a quantitative experimental research type, where the method is intended to test the influence of a variable or several variables on other variables in the research uses simulations on a program, software or application in applying BNCT for brain cancer therapy taken from several scientific sources and journals (Perona et al., 2020). The research method with simulation in the study used the PHITS application version 3.33 with the neutron source simulation used was the 30 MeV Cyclotron (a cyclotron type accelerator operated with an energy of 30 MeV) with a thermal neutron flux value of 1,8 x 10^9 n/cm^2/s.

Patient Modeling
The modeling of patients and cancer cells using the ORNL-MIRD phantom of an adult male with a type of brain cancer is Glioblastoma Multiforme, with a cancer size of 2 cm in radius and 4 cm in diameter at a depth of 7 cm from the upper surface of the head (Ganjeh & Kalantari, 2019).

Target Volume
In the International Commission on Radiation Units and Measurement (ICRU) guidelines for the target volume of irradiation on cancer cells, it is divided into 3 layers, as follows Planning Target Volume (PTV), Clinical Target Volume (CTV) and Gross Target Volume (GTV). Based on its definition, GTV is the core of the cancer cell volume where the area is detected as the position of cancer with the highest density of cancer cells and is clearly visible to the eye and can be felt. CTV is an area that has the potential to be infected by subclinical and microscopic cancer cells. This area is also the GTV area plus the volume around the GTV where the cancer spreads. PTV is a target area designed according to data that already has a geometric concept based on clinical and physical. This area is the CTV area plus additional boundaries for radiation treatment planning and evaluation (Toussaint et al., 2023).

The size of the radius on the GTV organ or cancer cells is 2 cm, the CTV is 3 cm and the PTV is 4 cm, the brain is 7 cm, the skull is 8 cm and the skin is 9 cm. The comparison of boron-10 concentration in the GTV organ is 100%, then the CTV is varied by 50% or twice as much as the amount of boron concentration given to the GTV organ, then the boron concentration in the PTV organ and other organs is varied by 10% or ten times more than the boron concentration in the GTV organ (Ramadhani et al., 2020).

Instrument and Material
The research using instruments including : Laptop, some applications or software, such as Particle and Heavy Ion Transport code System (PHITS) v3.33, Ghostscript v10.03.1, GSview v5.0, Notepad++ v8.6.4, Sumatra PDF Reader v3.5.2, Microsoft Excel 2021, Microsoft Word 2021. The materials used are boron-10 called BSH and BPA with boron concentrations of 20 μg/g, 40 μg/g and 60 μg/g cancer tissue. (Imperio & Panza, 2022).

Research Variables
The variables in this simulation consist of independent variables, dependent variables and controlled variables. The independent variables in the study were boron-10 concentrations of 20 μg/g, 40 μg/g and 60 μg/g of cancer tissue. Then, the dependent variables in the study are the boron dose rate, irradiation time and absorbed dose, then the controlled variables in the study are the thermal neutron flux values in cancer cell organs with values and controlled at 1,8 x 10^9 n/cm^2/s.

Data Analysis Technique
The research to find out the number of atoms with Equation 1 (Fadzilah, 2018).

$$N_{i-tissue} = \frac{\frac{m_i}{Ar_i} . N_A}{m_{tissue}} \quad (1)$$

where $N_{i-tissue}$ is number of atoms per 1 kg of tissue (atoms/kg), N_A is avogadro's number (6,023 × 10^{23} atoms/mol), m_i is mass of atom (g), m_{tissue} is mass of tissue (kg), Ar_i is relative atomic mass of elements (g/mol).

The mass of tissue value can be obtained using Equation 2 (Ramadhan, 2018).

$$m_{tissue} = V \times \rho \tag{2}$$

Where m_{tissue} is mass of tissue (kg), V is volume (m^3), and ρ is density (kg/m^3)

The volume of organs and cancer cells using Equation 3 (Ramadhan, 2018).

$$V = \frac{4}{3} \times \pi \times r^3 \tag{3}$$

where V is volume (cm^3), $\pi = \frac{22}{7}$, and r is radius (cm).

The mass of boron-10 is obtained using Equation 4 (Fadzilah, 2018).

$$m_{boron-10} = \frac{concentration_{boron-10} \times m_{tissue}}{ratio} \tag{4}$$

where $m_{boron-10}$ is mass of boron (g), $concentration_{boron-10}$ is boron concentration (μg/g), and $ratio$ is comparison of each cell

The boron dose rate is the result of the reaction of thermal neutrons with boron-10. The boron dose rate can be obtained using Equation 5 (Fadzilah, 2018).

$$\dot{D_B} = \frac{\Phi \,.\, N_{B10-tissue} \,.\, \sigma_{a,B10} \,.\, Q(1{,}6 \times 10^{-13})\, J/MeV}{1\, J.Kg^{-1}/Gy} \tag{5}$$

where $\dot{D_B}$ is boron dose rate (Gy/s), Φ is thermal neutron flux (neutrons/cm^2/s), $N_{B10-tissue}$ is number of boron-10 atoms per tissue mass (atoms/kg tissue), $\sigma_{a,B10}$ = Cross section of boron-10 absorption (3,8637 × 10^{-21} cm^2), and Q is particle energy (MeV).

Irradiation time is the minimum dose value divided by the boron dose rate during irradiation of cancer cells over a certain period of time. The irradiation time is obtained using Equation 6 (Fadzilah, 2018).

$$t = \frac{D_{minimum}}{\dot{D}_{cancer\ cells}} \tag{6}$$

where t is irradiation time (s), $D_{minimum}$ is minimum dose to destroy cancer cells (Gy), $\dot{D}_{cancer\ cells}$ is boron dose rate on cancer cells (GTV) (Gy/s).

Absorbed dose is the rate of boron dose absorbed by the tissue multiplied by the irradiation time. The absorbed dose in tissue can be obtained using Equation 7 (Fadzilah, 2018).

$$D_{absorb} = \dot{D}_{tissue} \times t \tag{7}$$

where t is irradiation time (s), D_{absorb} is dose absorbed by tissue (Gy), and $\dot{D}_{tissue}$ is boron dose rate on tissue (Gy/s).

Procedure

The procedure of the research, as follows :

1. Searching for literature and references on the BNCT method for brain cancer.
2. Creating the geometry of organs and cancer cells according to the shape, size and position of the organ using the PHITS input code.
3. Calculating the volume of organs in this study that were calculated were the skin, skull, brain, PTV, CTV and GTV.
4. Varying the boron concentration including 20 μg/g, 40 μg/g and 60 μg/g of cancer tissue and an energy source of 30 MeV, then click Save.
5. Running the PHITS application, the input code is saved in notepad++ with the format *.inp file, then right-click => Send to => PHITS using the Command Prompt (CMD) application.

6. The results of running the PHITS application, obtain an output file in the form of a PHITS code with the format *.out file, which is stored in Notepad++.
7. Calculating the boron dose rate, irradiation time and absorbed dose based on variations in boron concentration in each organ.
8. Displaying output files in the form of images and geometry in files with *.eps file format using GSview v5.0.
9. The results are analyzed using Microsoft Excel to display data in the form of graphs, then discussed and concluded.

Result and Discussions

Geometry of Brain Cancer Organs and Cells

The geometry of these organs is spherical, such as the light brown is skin organ has a radius of 9 cm, then the gray is skull bone has a radius of 8 cm and the pink is brain has a radius of 7 cm, then the yellow is PTV has a radius of 4 cm, then the orange is CTV has a radius of 3 cm and the red is GTV has a radius of 2 cm can be seen in Figure 1, while in a three-dimensional (3D) view in Figure 2.

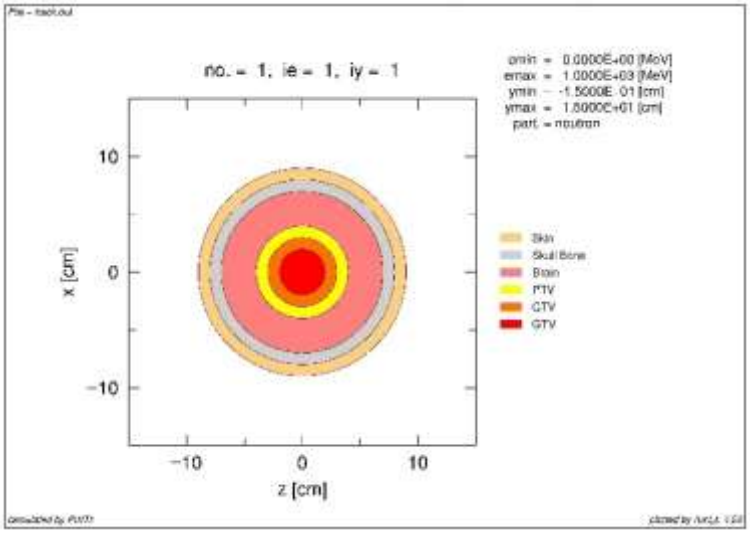

Figure 1. Geometry Simulation of Brain Cancer Organs and Cells (Glioblastoma Multiforme)

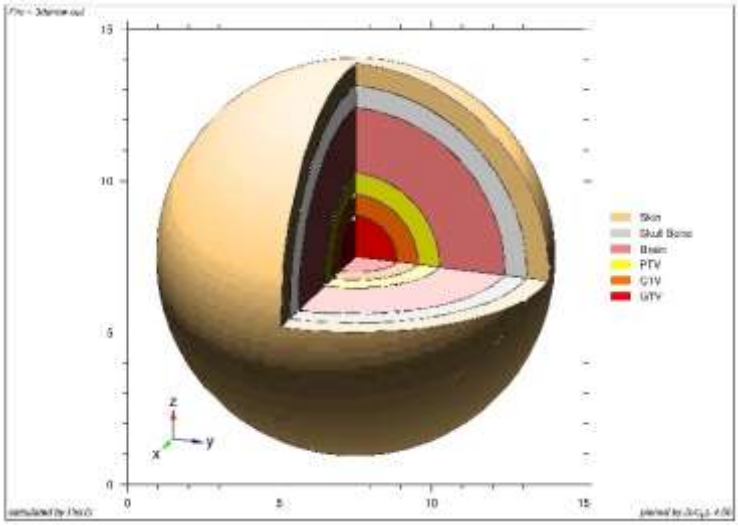

Figure 2. Geometry Simulation of Brain Cancer Organs and Cells (Glioblastoma Multiforme) in 3 Dimensions

Neutron Flux Irradiation

There are 3 variations of boron-10 concentration used, namely 20 μg/g, 40 μg/g and 60 μg/g of cancer tissue. Thermal neutron flux is a controlled variable whose value is made constant or fixed. Because of

that, the simulation of boron concentration at 40 µg/g and 60 µg/g of cancer tissue, the simulation results remain the same. The simulation results show that the neutron flux distribution simulation in brain cancer cells with a simulation example of boron concentration of 20 µg/g can be seen in Figure 3. It shows a simulation of the neutron flux spreads most to the cancer cells (green) located in the center of the circle.

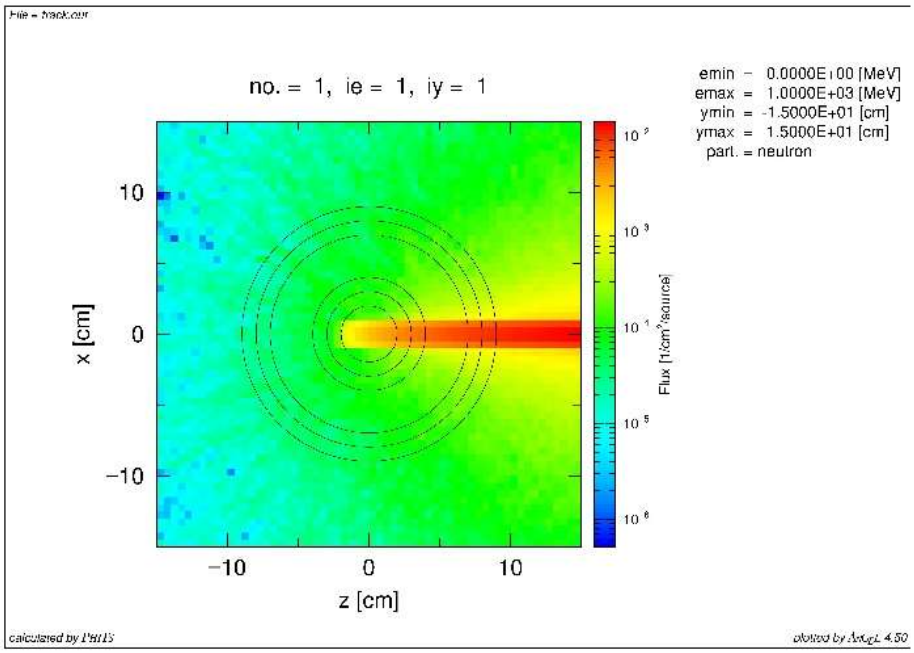

Figure 3. Simulation of Neutron Flux Irradiation on Brain Cancer Cells with Boron Concentration in 20 µg/g Cancer Tissues

Boron Dose Rate

The boron dose rate can be determined from the reaction results between thermal neutrons and boron-10, as in Equation 5 (Fadzilah, 2018). The results of the calculation of the boron dose rate values from each organ with 3 variations of boron concentration, as follows 20 µg/g, 40 µg/g and 60 µg/g of cancer tissue can be seen in the boron dose rate value table in Table 1. The table shows that the boron dose rate value is higher in the deepest layer of the cancer organ and lower in the outermost layer of the cancer, then the greater the boron concentration, the greater the boron dose rate value in each organ.

Table 1. Boron Dose Rate Value

Boron Concentration (µg/g)	Boron Dose Rate (Gy/s)					
	Skin	**Skull Bone**	**Brain**	**PTV**	**CTV**	**GTV**
20 µg/g	3,718E-03	3,719E-03	3,720E-03	3,721E-03	1,859E-02	3,719E-02
40 µg/g	7,437E-03	7,439E-03	7,440E-03	7,441E-03	3,718E-02	7,437E-02
60 µg/g	11,156E-03	11,158E-03	11,159E-03	11,160E-03	5,578E-02	11,160E-02

The table can be proven through the graph, as shown in Figure 4, it shows the highest boron dose rate value of 1,1160E-01 Gy/s or 11,160 x 10-2 Gy/s at a boron concentration of 60 µg/g in the GTV organ, while the lowest boron dose rate value is 0,3718E-02 Gy/s or 3,718 x 10-3 Gy/s at a boron concentration of 20 µg/g in the skin organ.

The factors causing the highest boron concentration value and boron dose rate value in the GTV organ are because the GTV organ is where the center of cancer cells is located and the large amount of boron concentration value is also absorbed by cancer cells so that the boron reaction captures thermal neutrons causing the decay of boron-10 to change into alpha particles and lithium-7, the number of these particles increases and their energy increases, especially alpha particles to destroy cancer cells. Therefore, the greater the concentration, the greater the dose rate in the GTV.

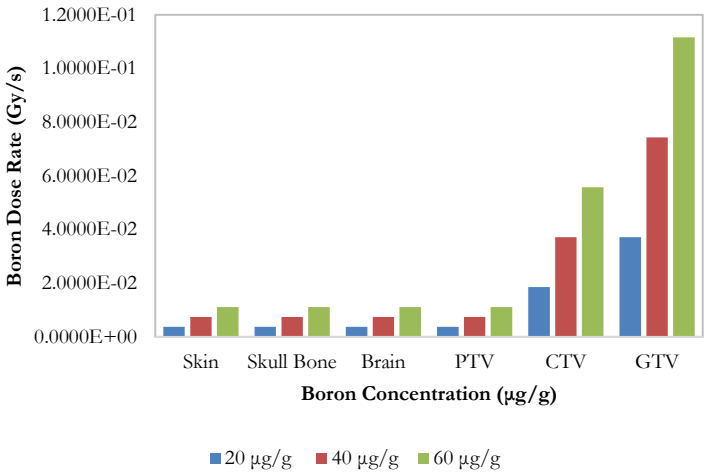

Figure 4. Boron Dose Rate Value Graph for Each Organ

Furthermore, the factor that cause lowest boron concentration value and boron dose rate in the skin organ is because there is no indication of cancer in this organ and there is no radiation reaction between thermal neutrons and boron-10 in the skin organ, thus minimizing boron radiation on healthy tissue around it and the boron dose rate that reacts in the skin organ is very small, as well as in other organs, such as the skull, brain and PTV.

The difference between the lowest boron dose rate value of 3,718 x 10^{-3} Gy/s and the highest of 11,160 x 10^{-2} Gy/s is that the lowest dose rate value on the skin organ has small energy and the strength of radiation exposure to the organ is also small because there is no thermal neutron reaction with boron-10, while the highest dose rate value on the GTV organ has large energy and the strength of radiation exposure to the organ is also large because of the thermal neutron reaction with boron-10 which produces alpha particles with large energy.

The effects caused by the lowest boron dose rate value on the skin organ are safe, while the effects caused by the highest boron dose rate value on the GTV organ are to selectively destroy cancer cells without damaging healthy tissues around them. Thus, the higher the boron concentration, the higher the boron dose rate value on each organ. The boron dose rate value increases with increasing boron concentration, especially in the deepest layers of cancer cells.

The highest boron dose rate value is in the GTV organ because BNCT therapy has a selective nature where cancer cells contain high boron-10 compared to other organs so that it can destroy cancer cells, while the boron dose rate value in organs other than cancer cells, such as skin, skull bones, brain, PTV and CTV and the outermost layer of cancer tends to have a low boron dose value and is almost the same because it does not damage healthy organs around it (Laudensia et al., 2020).

This is in accordance and proven for the boron dose rate value in the GTV organ that the highest boron dose rate value is in the cancer center itself, namely the GTV organ with a value of 1,1160 x 10^{-1} Gy/s or 11,160 x 10^{-2} Gy/s in one second.

The boron dose rate value is directly proportional to the boron concentration which can be proven by the graph, as in Figure 5, it shows that the higher the concentration of boron in GTV (cancer cells), the higher the value of the boron dose rate in GTV. The graph is drawn linearly as a trendline to determine the level of relationship between boron concentration and boron dose rate. The correlation coefficient shows $R^2 = 1$ which means perfect, meaning that the boron concentration has a very big influence and is directly proportional to the boron dose rate. This causes the level of relationship to show a perfect value (Mustafa, 2023).

Irradiation Time

The irradiation time is obtained from Equation 6 in the form of a comparison between the minimum dose of brain cancer cell damage and the dose rate of cancer cells. The minimum dose of damage is 30 Gy (Ramadhan, 2018). The results of irradiation time data on the GTV organ can be seen in the irradiation time table in Tabel 2. The table shows that the higher the boron concentration, the faster the

irradiation time. In the table, the shortest time is 4 minutes 48 seconds at a concentration of 60 µg/g. The irradiation time value is inversely proportional to the boron concentration.

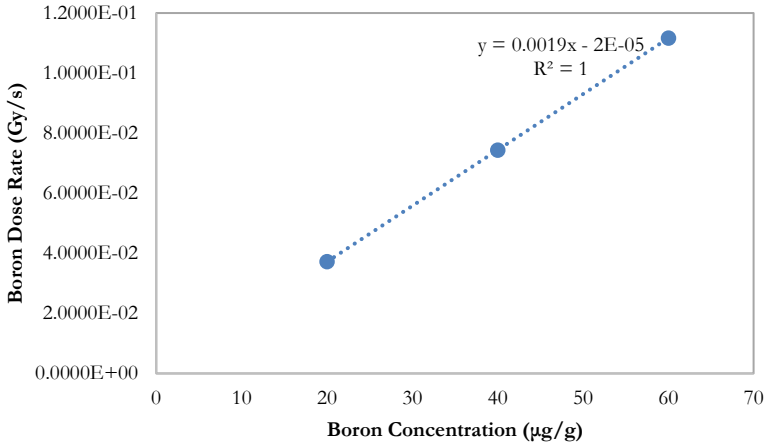

Figure 5. Graph of Boron Dose Rate Value against Boron Concentration in GTV

Table 2. Irradiation Time

Boron Concentration (µg/g)	Boron Dose Rate (Gy/s)	Irradiation Time (s)	Irradiation Time	
			minute	second
20 µg/g	3,719E-02	806,668	13	44
40 µg/g	7,437E-02	403,388	7	12
60 µg/g	11,160E-02	268,817	4	48

The table 5 can be proven through the graph, as shown in Figure 6, it shows that the higher the concentration of boron in GTV (cancer cells), the faster the irradiation time in GTV. The graph is drawn a logarithmic trendline to determine the level of relationship between boron concentration and irradiation time. The correlation coefficient shows R2 = 0.9984 which means very strong, meaning that the boron concentration has a very strong influence and is inversely proportional to the irradiation time. This causes the level of relationship to show a very strong value (Mustafa, 2023).

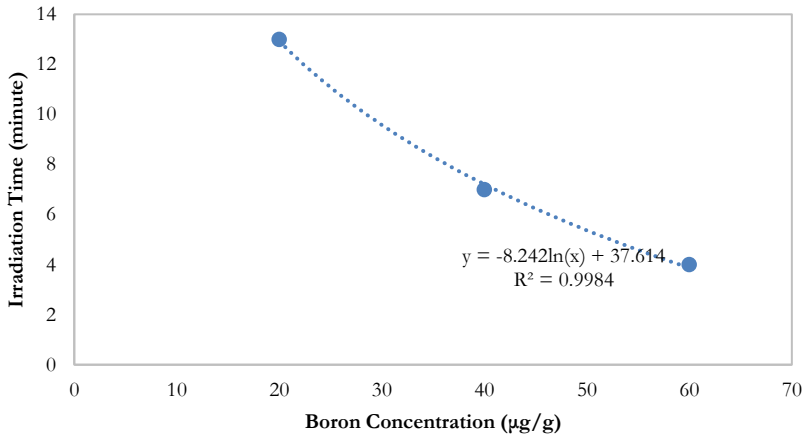

Figure 6. Graph of Irradiation Time against Boron Concentration in GTV

Absorbed Dose

The absorbed dose is obtained from the dose rate multiplied by the irradiation time, as in Equation 7. The results of the calculation of the absorbed dose in each organ can be seen in the table of absorbed

doses for each organ in Table 3. The table shows the highest value of the boron dose absorbed in the GTV organ as the center of cancer cells is 30 Gy (Ramadhan, 2018).

In the other organs some have the same absorbed dose value because the concentration of boron absorbed and has damaging properties only on cancer cells, not on healthy tissue and the area with the highest absorbed dose in the GTV organ and the difference in size of each organ is not much.

Table 3. Absorbed Dose Value of Each Organ

Boron Concentration (µg/g)	Absorbed Dose (Gy)					
	Skin	Skull Bone	Brain	PTV	CTV	GTV
20 µg/g	2,99	3,00	3,00	3,00	14,99	30,00
40 µg/g	2,99	3,00	3,00	3,00	14,99	30,00
60 µg/g	2,99	2,99	2,99	2,99	14,99	30,00

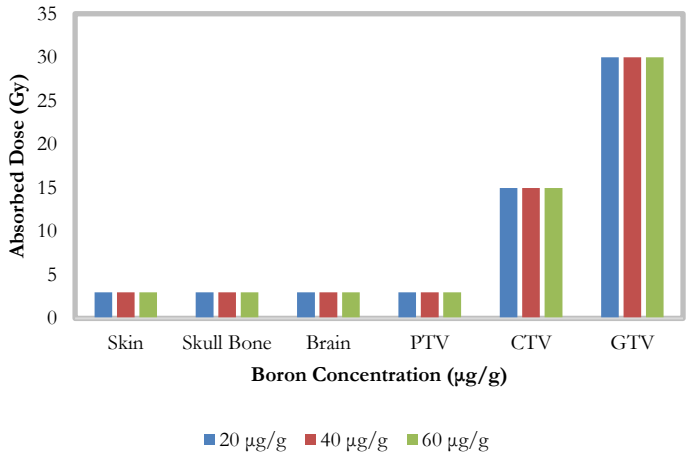

Figure 7. Absorbed Dose Value Graph for Each Organ

Figure 7 shows that the highest absorbed dose is in the deepest organ located in the middle of the cancer cells, while the absorbed dose is low and almost the same in the outermost organ of the cancer cells because the organ containing cancer cells only absorbs a lot of boron concentration compared to the healthy organs around it where no cancer cells are found. With these results, BNCT can be applied to the treatment of cancer patients, especially brain cancer.

Conclusion

The higher the boron concentration, the greater the boron dose rate for brain cancer treatment. In this case, boron concentration of 60 µg/g cancer tissue, a boron dose rate value of 11,160 x 10-2 Gy/s was produced in the GTV organ. The boron dose rate value increased in the cancer cells. The higher the boron concentration, the faster the irradiation time for brain cancer treatment. At a boron concentration of 60 µg/g cancer tissue, a very short irradiation time was obtained in only 4 minutes 48 seconds. The higher the boron concentration, the greater the absorbed dose for brain cancer treatment. The highest absorbed dose was 30 Gy in the deepest organ, namely the GTV organ where cancer cells are located.

Acknowledgments

The researcher would like to thank the Department of Physics, Universitas Islam Negeri Walisongo Semarang.

Conflicts of interest

The authors affirm that they have no conflicts of interest.

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