Dose Analysis of Boron Neutron Capture Therapy (BNCT) Treatment for Lung Cancer Based on Particle and Heavy Ion Transport Code System (PHITS)

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KEYWORDS

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ABSTRACT The objectives of this study were to determine the effect of boron concentration on total dose rate for lung cancer treatment, and to determine the effect of boron concentration on the length of irradiation time for lung cancer treatment. This study was computer simulation-based using the Particle and Heavy Ion Transport code System (PHITS) by defining the geometry and components of lung cancer and the surrounding organism as the object being studied and the source of radiation used. The type of phantom used was the ORNL of an adult Asian male. The neutron source used was Kartini Reactor. The independent variable was the boron concentration of 30, 40, 50, 60, and 70 $\mu\text{g/g}$ cancer tissue and the dependent variables were the dose rate and the irradiation time. The results of this study indicated that the larger the amount of boron concentration that was injected, the higher the rate of total dose the organ received, where the total dose rate for each variation of boron concentration were 1.34×10^{-3} Gy/s, 1.71×10^{-3} Gy/s, 2.07×10^{-3} Gy/s, 2.42×10^{-3} Gy/s, and 2.78×10^{-3} Gy/s, and the larger the amount of boron concentration that was injected, the faster the irradiation time for the treatment of lung cancer was, where the irradiation time required for each variation of boron concentration was 37294 s, 29240 s, 24180 s, 20633 s, and 17996 s.

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1. INTRODUCTION

Cancer is a deadly malignant disease and one of the leading causes of death worldwide (WHO 2017b). Cancer occurs from changes in cells that grow abnormally and uncontrollably. These cells then spread and grow to develop in new places, which eventually become cancer cells (Cancer Research UK 2017). Heart disease and cancer are the first and second leading causes of death in the world. A study by Weir et al. (2016) showed that the overall rate of deaths from heart disease declined rapidly since 1960, whereas deaths associated with cancer increased. Since the risk of death from heart disease is declining more sharply than cancer, it is likely that if this trend continues, cancer will become the main cause of death in the future (Weir et al. 2016).

Lung cancer is the leading cause of cancer-related deaths in men and the second leading cause of cancer-related deaths in women worldwide. In 2012, 1,589,800 deaths were reported worldwide (Pakzad et al. 2015). There were 1.69 million cancer-related deaths in 2015 (WHO 2017b). Lung cancer is the most common form of cancer in Asia with 1,033,881 lung cancer cases, 926,436 of which were fatal (Chan and Hughes 2015). According to WHO's data in 2014, lung cancer is also the most prevalent type of cancer in Indonesia, with a percentage of 21.8% and a total of 22,476 deaths (Stewart and Wild 2014). Lung cancer is also one of the top five diseases present in the world as a whole (WHO 2017a).

Although progress has been made in biomedical research, diagnostics, and therapeutic options the past few decades, lung cancer still has a poor prognosis, with more than half of all patients diagnosed with this disease dying within a year of their diagnosis, and only 18% of survivors living up to or beyond five years (Calabuig-Fariñas et al. 2016). There are two major subtypes of lung cancer, namely Small-Cell Lung Carcinoma (SCLC) and Non-Small-Cell Lung Carcinoma (NSCLC), covering 15% and 85% of all lung cancers, respectively (Zappa and Mousa 2016). One cause of lung cancer is radon radioactive gas caused by tobacco smoke. Tobacco smoke contains more than 7000 chemical compounds that can cause DNA mutations, inflammation, free radicals, and genetic changes in humans (Stewart and Wild 2014).

To date, the treatments that have been performed to combat cancer are oncologic surgery, chemotherapy, and radiotherapy, or a combination of these therapies. However, these treatments have not been fulfilled in both quality and quantity (Sardjono 2015). Surgical methods can not completely remove cancer cells and have the additional risk of causing pain and infection (Gomar et al. 2011; National Cancer Institute 2015). Methods of chemotherapy can kill or slow the growth of healthy cells that grow. Meanwhile, the radiotherapy method can damage healthy cells around the cancerous cells (Irwin and Cole 2011; National Cancer Institute 2015). Other new treatments developed to treat cancer are hormone therapy and immunotherapy.

However, the treatment is unable to prevent the spread of cancer cells in the tissue and is only preventive (Wahyungingsih 2014). Research conducted by Zappa and Mousa (2016) showed that there are no significant advantages of the treatment because it still had poor side effects and the average overall survival for patients was only about 8–10 months.

Based on the weakness of the above cancer treatment methods that have an impact on the death of healthy cells, an alternative to cancer treatment should be selected that can prevent the spread of cancer cells, along with having a small risk of harm to healthy tissue. The method of therapy is Boron Neutron Capture Therapy (BNCT), known as the principle of selective targeting (Novitasari 2015; Wahyungingsih 2014).

BNCT is a radiotherapy that combines high biological targeting and LET radiation (Fariás et al. 2014). The ratio of B-10 concentration to cancer cells and healthy cells is 10:1, so the therapy is selective because the chances of neutrons reacting with the concentrated B-10 in the cancer cells is higher than in healthy cells (Sauerwein et al. 2012).

BNCT is based on neutron capture and fission reactions. Non-radioactive B-10 irradiated with thermal neutrons produces high energy particle LET (α), Li-7 and gamma rays (γ) (Zolfaghari and Sedaghatizadeh 2015). The B-10 and neutron reactions produce α particles with energy of $150 \text{ keV}\mu\text{m}^{-1}$ and Li-7 with energy of $175 \text{ keV}\mu\text{m}^{-1}$ (Moss 2014). After reacting with neutrons, B-10 changes to B-11 which is metastable. B-11 has a very short half-life of 10^{-12} s while Li-7 has a half-life of 10^{-5} s (Zolfaghari and Sedaghatizadeh 2015). Destructive effects occur in a very short time, with high LET in the 5–10 μm range in the tissue (Fariás et al. 2014). The LET trace is equivalent to a single cell diameter $< 10 \mu\text{m}$ (Barth et al. 2012).

In order to have a neutron capture reaction with a B-10 nucleus, a neutron source in accordance with International Atomic Energy Agency (IAEA) standards is required. There are two types of neutrons that can be used as a neutron source in BNCT, namely thermal neutrons and epithermal neutrons (Krstic et al. 2014a). Thermal neutrons are commonly used for cancer cells located on the surface of the skin (superficial). Epithermal neutrons are used for the treatment of cancer at a depth of 8–10 cm from the surface of the skin (Valleñry et al. 2015). Epithermal neutrons will be moderated by body tissues (especially those with large amounts of water), thus arriving at cancer cells in the form of thermal neutrons. In order to be used for BNCT therapy

so as not to harm other healthy tissue, the source neutron must meet the neutron beam parameters such as the intensity of the epithermal neutrons and the quality of the beam (Sauerwein and Moss 2009).

Interest in BNCT has grown significantly in recent years (Bavarnegin et al. 2013). The development of BNCT technology and applications in the world has spread across 20 hospitals in 13 countries such as Finland, Japan, USA, the Netherlands, Sweden, Taiwan, China, Japan, South Korea, and several other countries. Currently, several countries around the world are focusing on developing BNCT research, including Indonesia (Sardjono 2015).

BNCT has been shown to have promise in combating lung cancer type NSCLC, providing a safe and potentially effective treatment. BNCT can be the potential solution to dealing with tumors that cannot be surgically removed or cannot be treated due to their location, stadium, or overall patient status (Fariás et al. 2014). Preclinical studies at the Massachusetts Institute of Technology (United States) have been conducted on small animals in order to assess normal lung tolerance to BNCT and understand the toxicity of the human lung during treatment (Kiger et al. 2004). In Japan, preclinical studies have shown that BNCT is feasible for treating lung cancer by using epithermal neutron sources (Matsumoto 2007), without causing toxicity in healthy lungs and other tissues involved (Suzuki et al. 2012). At the University of Pavia (Italy), a study of BNCT for pulmonary metastases in mouse models showed that the ratio between boron concentrations in tumors and in normal lungs was appropriate for safe and effective treatment (Bortolussi et al. 2011). This result is consistent with that of Trivillin et al. (2014), whose study showed that the value of boron concentration in the lungs is very useful either using BPA or GB-10 or a combination of them.

The accuracy of BNCT is determined by large doses to kill the cancer. One type of software that can perform dose calculations on BNCT is the Particle and Heavy Ion Transport code System (PHITS). PHITS is a newly developed Monte Carlo treatment planning system based on JAEA Computational Dosimetry System's (JCDS) basic technology (Kumada et al. 2009). It can be used to evaluate the doses absorbed into each organ in phantom reference (Petoussi-Henss et al. 2010) and calculate the particle track (Oktajianto and Setiawati 2016). The PHITS code has been used for research related to BNCT (Kumada et al. 2015; Takada et al. 2014).

2. MATERIALS AND METHODS

2.1 Patient model

The geometry of the lung organ was based on the Phantom Oak Ridge National Laboratory (ORNL) for adult men (Eckerman et al. 1996). The type of lung cancer selected was Non-Small-Cell Lung Cancer (NSCLC). The cancer cells were located in the middle of the right lobe of the lungs. This study was intended for patients with stage 1A lung cancer with a diameter of 3 cm (Tsim et al. 2010; Weaver and Coonar 2017), where the cancer was still in the lungs and had not yet spread to the lymph nodes, bronchi, muscle and the surrounding tissue.

The lung geometry was constructed from a half-elliptical shape that was reduced by the section removed. When the section removed on the left lung is greater than the right lung due to the position of the heart. Cancer cells consist of three parts, namely PTV, CTV, GTV. Cancer cells accumulate in GTV (Ardana and Sardjono 2017).

FIGURE 1. Phantom body (a) and cancer cell (b).

The phantom material consisted of three tissues, namely the lungs (blue), bone (green), and soft tissue (yellow), as shown in Figure 1 (Krstic et al. 2014b). The materials in the phantom were chosen to be as close as possible to the tissues of humans. Information on these materials is available from the report of the International Commission on Radiological Protection (ICRP).

B-10 concentration in CTV area varied by 50% of B-10 concentration which was given in the GTV area, whereas B-10 concentration in PTV area and other healthy tissue varied by 10% of B-10 concentrations given in the GTV area. In other words, the comparison of B-10 on each tissue was GTV:CTV:healthy tissue = 10:5:1. So, this therapy was selective because the chances of neutrons reacting with the concentrated B-10 in the cancer tissue was higher than in healthy tissue (Sauerwein et al. 2012).

The PHITS simulation was applied by irradiated of neutrons on the target of lung cancer. The neutron used was the output from the beam port of Kartini Reactor, Indonesia. The PHITS program was executed through the command prompt (cmd) by clicking right on the *.inp program file and then selecting send to > PHITS. PHITS performs calculations using the Monte Carlo method.

The output of the PHITS results was automatically saved in one folder with the program input file. The format of the output files is designated with the extensions *.eps and *.out. The extension *.eps shows the results in a graph that can be opened with the program Gsview64, while extension *.out shows the results in the form of data, which that can opened with Notepad++ or Excel. The result of running PHITS in this research was that there were three outputs, namely neutron flux data, dose rate neutron scattering, and neutron tracks. Flux data and track neutrons were determined using the Tally Cross calculation, whereas the dose of neutron scattering used Tally Track and multiplier calculations.

2.2 Beam source

The calculation of doses consisted of four parts according to the interactions that occur. The dose components included the alpha dose, proton dose, gamma dose, and scattering dose neutrons. Obtaining the alpha dose rate value, the proton dose rate, gamma dose rate, total dose rate, irradiation time, and absorption dose was achieved using the following stages.

2.2.1 Number of atoms in a tissue

The calculation of the number of atoms in 1 kg of tissue was performed using Equation 1.

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

where, $N_{i-tissue}$ is the number of elemental atoms i in a kilogram of tissue (atom/kg), m_i is the mass of element i (g), Ar_i is the mass number element i (g/mol), m_{tissue} is the mass of the tissue (kg), and N_A is Avogadro's constant with a value of 6.023×10^{23} atoms/mol.

2.2.2 Alpha and proton dose rate

The alpha dose is the result of the interaction between boron with thermal neutrons. The reaction produces alpha with a mean energy of 2.33 MeV. The dose of proton is the result of the interaction catch between boron neutron and

N-14. Proton with an average energy of 0.66 MeV. The dose rate of alpha and proton was calculated using Equation 2.

$$\dot{D} = \frac{\Phi \cdot N_{i-tissue} \cdot \sigma \cdot Q (1.6 \times 10^{-13}) \text{ J/MeV}}{1 \frac{\text{J/kg}}{\text{Gy}}} \quad (2)$$

where, $\dot{D}$ is the dose rate (Gy/s), Φ is the thermal neutron flux in the tissue ($\text{n.cm}^{-2}.\text{s}^{-1}$), $N_{i-tissue}$ is the number of atomic elements i in 1 kg of tissue (atom/kg), σ is a microscopic cross section (cm^2), and Q is the energy particle (MeV).

2.2.3 Gamma dose rate

Hydrogen in the tissue will interact with thermal neutrons. The catch rate reaction of thermal neutrons by this hydrogen are comparable with a hydrogen-2 formation rate. It is equivalent to the release rate of gamma with energy of 2.23 MeV. The gamma release rate was calculated using Equation 3.

$$\ddot{R} = \Phi \cdot N_{i-tissue} \cdot \sigma \quad (3)$$

where, $\ddot{R}$ is the rate of gamma release (γ/s), Φ is the thermal neutron flux ($\text{n.cm}^{-2}.\text{s}^{-1}$), $N_{i-tissue}$ is the number of atomic elements i in 1 kg of tissue (atom/kg), and σ is a microscopic cross section (cm^2). Consequently, the gamma dose rate can be calculated using Equation 4.

$$\dot{D}_\gamma = \ddot{R} \cdot \Delta \cdot \phi \quad (4)$$

where, $\dot{D}_\gamma$ is the rate of gamma dose (Bq/kg), Δ is the coefficient of absorption rate or activity specific (Gy.kg/Bq.s), and ϕ is a gamma-absorbing dose fraction.

2.2.4 Total dose rate

After obtaining the value of alpha dose rate, proton dose rate, neutron scattering dose rate, and gamma dose rate, the total dose rate can be calculated. In this study, the total dose rate had the same principle with the equivalent dose on radiation protection. The dose equivalent was obtained by multiplying the dose absorption by the radiation weight factor (Sardjono et al. 2016). The total dose rate was calculated using Equation 5.

$$\dot{D}_{total} = (w_\alpha \times \dot{D}_\alpha) + (w_p \times \dot{D}_p) + (w_n \times \dot{D}_n) + (w_\gamma \times \dot{D}_\gamma) \quad (5)$$

where, w_α is an alpha radiation quality factor, w_p is a proton radiation quality factor, w_n is a neutron scattering radiation quality factor, and w_γ is a gamma radiation quality factor. The radiation quality factor value is shown in Table 1.

TABLE 1. Radiation quality factor values.

Radiation source	Radiation factor
Alpha	3.8 (cancer tissue)
	1.3 (healthy tissue)
Proton	3.2
Neutron	3.2
Gamma	1.0

2.2.5 Irradiation time

The irradiation time is determined by the minimum dose of destroyer in cancerous tissue divided by the total dose rate (Equation 6). In this case the dose minimum damage to cancer tissue that is equal to 50 Gy.

$$\text{time irradiation (s)} = \frac{\text{dose minimum damage to cancer (Gy)}}{\text{total dose rate (Gy/s)}} \quad (6)$$

2.2.6 Absorption dose

After the irradiation time is determined, the dose received in the organ can be calculated. The total dose value can be analyzed to test whether it does not exceed the dose limit received by the healthy organ or Organ At Risk (OAR). The absorption dose was calculated using Equation 7.

$$\text{Dose (Gy)} = \text{dose rate (Gy/s)} \times \text{irradiation time (s)} \quad (7)$$

3. RESULTS AND DISCUSSION

3.1 Irradiation geometry

There has been a comparison between neutron irradiation in LLAT and AP to obtain an effective irradiation position in

FIGURE 2. Geometry of LLAT irradiation.

FIGURE 3. Geometry of AP irradiation.

lung cancer. The irradiation of the LLAT is from the right side of the body, in accordance with the position of the cancer located in the right lung, whereas the irradiation of the AP is from the front of the body just in the position of the cancer. The geometric results obtained from the program output show the difference in distance between irradiation with LLAT and AP against cancer. This is shown in Figures 2 and 3.

In the LLAT irradiation the distance on the primary cancer (GTV) with the neutron source is 10 cm, whereas in the AP irradiation, the distance on GTV with the neutron source is 3.5 cm. Therefore, for LLAT irradiation is not used because the distance to the cancer position is deeper and changes the value of neutron flux that reaches the cancer only slightly, as shown in Figures 4 and 5. In addition, the irradiation of LLAT is irradiated with a pass-through position of the heart organ, so the heart can be at risk of getting higher doses compared with the AP irradiation. So, in this study, selected geometry for irradiation of lung cancer that is AP (from the front of the body).

3.2 Neutron flux

The authors divide the energy neutrons range into three, namely thermal, epithermal, and fast. Thermal neutrons with energy ≤ 0.5 eV, epithermal neutrons with energy of 0.5 eV–0.02 MeV, and fast neutrons with energy ≥ 0.02 MeV. The characteristics of the neutron flux values received by each tissue are calculated per depth of the phantom of the body by assuming that the depth starts from zero from the point of irradiation.

FIGURE 4. Traces of neutrons in phantom on LLAT irradiation.

FIGURE 5. Traces of neutrons in phantom on AP irradiation.

Figure 6 is a cross-sectional image of a phantom body that is distinguished by lines to determine the tissue created. The division of phantom tissue aims to determine the amount of neutron flux for each of the depths reviewed. The surface of the skin is at a depth of 1.2 cm; rib at 1.6 cm; right lung at 2.8 cm; PTV tissue at 3.0 cm; CTV tissue at 3.2 cm; and GTV tissue at 3.5 cm.

Figure 7 is the result of flux value for 50 $\mu\text{g/g}$ boron concentration of cancerous tissue, whereas for other doses of cancer have similar values and flux characteristics.

Figure 7 shows that the flux value of epithermal neutrons at a depth of 0 cm is greater than that of the thermal neutron flux. The thermal neutron flux value is lower than the epithermal neutron flux because the energy that the thermal neutron has been exhausted during the journey to the tissue of body. The epithermal neutron flux increases first before flux decreases with increasing tissue depth. This occurs because the rapid neutrons interacting with the tissues decrease energy or moderation into epithermal neutrons.

Then the decrease of epithermal neutron flux is caused by scattering interactions with the constituent components of the tissue. This causes the epithermal neutron energy to decrease and change to thermal neutrons so that

FIGURE 6. Depth tissue in phantom.

FIGURE 7. Neutron flux in phantom.

the thermal neutrons increase to a depth of 2 cm. Then the thermal neutron flux value decreases as well as epithermal neutrons due to the absorption interactions with Hydrogen and Nitrogen atoms present in the tissue. The value of thermal flux also increased at a depth of 3.5 cm or the position where the main cancer (GTV) is located. This is because the percentage of boron on GTV is larger than other tissue.

3.3 Dose rate

The flux value is then used to calculate the rate of the alpha dose, proton dose, and gamma dose using Equations 1, 2, 3, and 4. Figure 8, is a value dose rate for 50 $\mu\text{g/g}$ boron concentration display the value of each dose component, namely alpha, protons, neutrons and gamma per organ, whereas in other boron concentrations has the same characteristic as Figure 8, differ only in the rate of alpha dose.

A significantly increased dose is the rate of alpha dosage. This is because of alpha radiation which plays a major role in killing cancer cells. The rate of alpha dosage only increases in CTV and GTV tissue, whereas in healthy tissue it does not increase. This is because the concentration of B-10 in the cancer tissue is much higher when compared with other healthy tissues. In other words, the absence of B-10 in healthy tissue, thus causing radiation caused between neutrons with B-10, do not occur in healthy tissue. This is in accordance with what is expected to minimize the dose received in healthy tissue.

FIGURE 8. Dose rate per organ.

FIGURE 9. Total dose rate per organ per boron concentration.

The total dose rate received by each tissue was calculated using Equation 5. The total dose rate per boron concentration and each organ is shown in Figure 9.

The correlation between the total dose rate and the boron concentration absorbed in cancer tissue is shown in Figure 10.

The larger the amount of boron concentration that was injected, the higher the rate of the total dose the organ received (as shown in Figure 10). The correlation between boron concentration and the dose rate value is linear with the following equation.

$$y = (2.69729 \times 10^{-4}) + (3.58861 \times 10^{-5}) x \quad (8)$$

Equation 8 can be used to calculate the value of the total dose rate received by cancer tissue, for other boron concentrations.

3.4 Irradiation time

The total dose rate is then used to determine the irradiation time to damage cancer tissue. The minimum dose of damage to cancer tissue is 50 Gy. So, to calculate the irradiation time is the minimum dose of 50 Gy destroyer divided by the total dose rate. The correlation between boron concentration and irradiation time is shown in Figure 11.

The larger the amount of boron concentration that is injected, the faster the irradiation time for the treatment

FIGURE 10. Correlation of boron concentration with dose rate.

FIGURE 11. Correlation of boron concentration with irradiation time.

of lung cancer is. The correlation of boron concentration with irradiation time is decreasing exponentially with the following equation.

$$y = (78432.86852) e^{(-\frac{x}{25})} + 13054.2381 \quad (9)$$

Equation 9 can be used to calculate the length of time of lung cancer irradiation treatment for other boron concentrations.

3.5 Absorption dose

The dose rate value is then used to calculate the dose value received by the organ. The dose value is obtained from the multiplication between dose rates and irradiation time. Cancer therapy with BNCT method, neutron radiation is done through a single fraction that is by way of one-time radiation. Because the radiation dose to kill cancer tissue is so large that it is equal to 50 Gy, it is necessary to pay attention to the dose received by the surrounding healthy tissue when therapy is carried out. It is expected that the doses received by healthy tissue around the cancer tissue remain below the tolerance limit of the dose received by the healthy tissue.

Healthy tissue used as an indicator of damage is healthy skin and lungs in the right lobe. The dose tolerance limit on the skin is 3 Gy. When exceeding the dose limit, the effects to be received on the skin are usually erythema, dry desquamation, wet desquamation, and necrosis. Tolerance limit for lung is 7.5 Gy. If it exceeds the tolerance limit, the lung will have pneumonitis.

Table 2 shows that at 30 µg/g boron concentration, the skin will have an erythema effect that exceeds the dose limit of 3 Gy. The effects of this erythema can be redness or the the formation of a rash, accompanied by itching according to the reaction of the patient's body condition. The effects of erythema only occur temporarily within a few hours (around 6-24 h). In addition, the lungs will also get pneumonitis or inflammation because they exceed the dose limit of 7.5 Gy. At 40 µg/g boron concentration, the skin dose is still below the safe limit, whereas the lung tissue will be affected by pneumonitis.

Concentrations of 50, 60 and 70 µg/g, both skin and lungs are still below the safe limit. Therefore, boron with a concentration greater than 50 µg/g to the maximum extent of administering boron in the body to BNCT is more recommended in the treatment of lung cancer, because it produces radiation exposure to smaller healthy tissues and requires shorter irradiation time.

TABLE 2. Dose on organ at risk (OAR).

Boron concentration (µg/g cancer tissue)	OAR	Absorbed dose (Gy)	Dose tolerance (Gy)
30	Lung	9.33	7.50
	Skin	3.17	3.00
40	Lung	7.73	7.50
	Skin	2.66	3.00
50	Lung	6.71	7.50
	Skin	2.34	3.00
60	Lung	6.00	7.50
	Skin	2.12	3.00
70	Lung	5.48	7.50
	Skin	1.96	3.00

4. CONCLUSIONS

The larger the amount of boron concentration that is injected, the higher the rate of total dose the organ received, where the total dose rate for each variation of boron concentration are 1.34×10^{-3} Gy/s, 1.71×10^{-3} Gy/s, 2.07×10^{-3} Gy/s, 2.42×10^{-3} Gy/s, 2.78×10^{-3} Gy/s. The larger the amount of boron concentration that is injected, the faster the irradiation time for the treatment of lung cancer is. The irradiation time required for each variation of boron concentration was 37294 s (10 h 21 min 34 s), 29240 s (8 h 7 min 20 s), 24180 s (6 h 43 min 0 s), 20633 (5 h 43 min 53 s), and 17996s (4 h 59 min 56 s).

The geometry of the phantom of the organs of the body is made more precise and specific perhaps like the approach to phantom voxel. A reference study is carried out in the medical aspect to find out the deeper biological conditions of the patient. An analysis was performed on larger boron concentrations.

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