

Investigation of Dose Enhancement in Lung Cancer Treated with Boron Neutron Capture Therapy

Shinde Sachin Babasaheb ¹

¹ Research Scholar, Department of Chemistry, Mansarovar Global University,
Sehore, M.P., India.

Dr. Neelu Jain ²

² Supervisor, Department of Chemistry, Mansarovar Global University,
Sehore, M.P., India.

ABSTRACT

An innovative method of targeted radiation therapy, boron neutron capture therapy (BNCT) makes use of the high linear energy transfer particles created when low-energy neutrons engage with boron-10 that has built up in malignant tissue. The current research assessed BNCT for lung cancer using a thorough computational dosimetric assessment. We used the correct RBE and CBE factors specified by ICRP to convert the gamma-ray, fast neutron, thermal neutron, and boron dose components to photon-equivalent dose. Then, we estimated the total absorbed dose. The findings show that neutron energy and boron concentration strongly affect the dosage distribution. The tumor was dosed more effectively with lower-energy neutrons, especially those with energies around 100 eV, whereas healthy organs in the vicinity received relatively lesser doses. Organs close to the radiation source were exposed to a considerable dosage, whereas those further away were exposed to a negligible amount. Based on the results, optimizing neutron energy and boron absorption can greatly enhance treatment effectiveness and tumor selectivity.

Keywords: Boron Neutron Capture Therapy, Lung Cancer, Energy; Organ, Dose.

I. Introduction

In spite of ongoing improvements in both diagnosis and treatment, lung cancer continues to rank among the most common and deadly forms of cancer globally, causing a disproportionate share of cancer-related deaths and illnesses. A large majority of cases are classed as non-small cell lung cancer (NSCLC), whereas a smaller percentage are classified as small cell lung cancer (SCLC). The absence of early symptoms and the limitations of standard screening procedures caused by the complicated anatomical structure of the lungs mean that the illness is generally identified at an advanced stage. Surgery, radiotherapy, chemotherapy, targeted therapy, and immunotherapy are

some of the standard treatment options. While they have improved survival rates in some patient populations, they often come with side effects like resistance and suboptimal tumor control, especially in advanced or recurrent cases. Despite its central role in lung cancer treatment, radiotherapy has its limitations due to the radiosensitivity of neighboring normal tissues, including the spinal cord, healthy lung parenchyma, and the heart. This limits the maximal dose that can be delivered to the tumor. To overcome these obstacles, researchers have been hard at work developing more targeted therapy strategies that can increase tumor cell death with less collateral harm to healthy organs.

A novel approach to radiotherapy, boron neutron capture treatment (BNCT) provides a selective mechanism for the eradication of tumors. It is a physiologically tailored and encouraging kind of radiation therapy. BNCT works by exposing tumor cells to low-energy thermal or epithermal neutrons, which trigger a nuclear process involving non-radioactive boron-10 (^{10}B) atoms that have collected preferentially within the cells. These two types of nuclei, recoiling lithium-7 (^7Li) and high-linear energy transfer (LET) alpha particles (^4He), are created by an encounter with a path length of around 5-10 micrometers, which is about the same as the diameter of a single cell. Therefore, the cytotoxic effects mainly target cells that contain boron, while normal tissues nearby are spared. When it comes to treating malignancies near vital organs, such lung cancers, BNCT stands out from traditional external beam radiation thanks to its unique cell-level selectivity.

The complicated anatomical and physiological features of the thoracic area make the application of BNCT in the treatment of lung cancer particularly intriguing. Traditional radiation may have less of an impact on lung cancers because of their uneven forms, varied cellular makeup, and fluctuating oxygenation. Another obstacle to precise dosing is the constant twitching of the lungs that occurs during breathing. Instead of depending just on geometric dosage distribution, BNCT's biological targeting mechanism concentrates the therapeutic impact at the cellular level, which might help it overcome some of these constraints. Even in situations where typical radiation dosages are constrained by normal tissue tolerance, BNCT might accomplish effective tumor control if enough concentrations of ^{10}B can be targeted to cells in lung tumors.

Creating and delivering boron-containing drugs with tumor tissue selectivity and poor absorption in normal cells is essential for BNCT to be a success. Substances like sodium borocaptate (BSH) and boronophenylalanine (BPA) have been extensively studied and tried in clinical settings for use in glioblastoma and head and neck tumors, among others. Investigating new boron carriers such nanoparticles, liposomes, and tumor-specific ligands, as well as enhancing the boron drugs' pharmacokinetics, intracellular retention, and tumor selectivity in the setting of lung cancer, are all areas of active study. These developments are essential for optimizing BNCT's therapeutic ratio, which improves the treatment's clinical viability and efficacy in thoracic cancer.

For lung cancer patients undergoing BNCT, precise dosimetry and careful planning of therapy are also crucial. In contrast to traditional radiation treatment, BNCT uses a combination of neutrons (both thermal and epithermal), gamma rays, and secondary charged particles produced when neutrons contact with tissue components. Consequently, the total absorbed dosage is the result of a complicated interplay between several dose components, the radiobiological efficacy of which

varies. Dose distribution estimation and treatment parameter optimization are two areas that saw a rise in the use of sophisticated computer models, mathematical phantoms, and Monte Carlo simulation methods. To guarantee an appropriate dosage to the tumor while sparing surrounding normal structures, accurate dosimetric assessment is crucial in lung cancer due to the high effect of tissue heterogeneity and air cavities on neutron transport.

From a therapeutic standpoint, BNCT may be beneficial for lung cancer patients with recurring or radio-resistant illness, as well as those who are not good surgical candidates. Potentially better local control and fewer treatment-related problems could result from its capacity to target tumor cells with high-LET radiation. Furthermore, BNCT can be used with other treatment methods, including immunotherapy or chemotherapy, to create a more effective and efficient treatment plan. While there has been less clinical experience with BNCT in lung cancer compared to other tumor locations, there is promising preclinical research and rising clinical indications that it might be a new alternative for treatment.

II. Review of Literature

Namdev, Shruti & Kaur, Gurmeet. (2022) In today's world, cancer is definitely a serious and perhaps fatal disease. In the United States, around 1.7 million people were diagnosed with cancer in 2017. One method that makes use of boron to treat cancer is BNCT, or Boron Neutron Capture Therapy. This method relies on the nuclear capture and fission process, which produces a variety of particles like Li and He nuclei together with their kinetic energy and γ -radiation, and is used as an analeptic. These radiations eliminate cancer cells while sparing healthy cells. By reducing their concentration in healthy cells, boron particles were delivered preferentially to cancer cells. Various types of cancer, including lung, brain, head/neck, hepatic, and gastrointestinal cancers, are the focus of clinical trials and research in this article. Recently discovered boron delivery agents and various approaches of their dosage distribution explain several methods of boron agent administration in tumor cells. Recent years have seen an uptick in the use of boron compounds in combination with other peptides, nanoparticles, EGFRs, liposomes, and copolymers in an effort to enhance the killer characteristics of these substances against specific cancer cells. As previously mentioned, BNCT is also useful in the treatment of certain cancers. In order to help readers understand how BNCT (Reactor-Based) works to cure cancer cells, this article has been written.

Zabihzadeh, Mansour et al., (2021) The interaction between neutrons and the nucleus, as well as the generation of heavy particles, makes them a more effective therapy than photons for hypoxic tumors. Boron neutron capture therapy (BNCT) was the target of this investigation because of its potential usefulness in the treatment of lung cancer. This was accomplished by determining the neutron dose distributions in terms of lung tumor volume and OARs, or peripheral organs at risk. In order to treat lung cancer, the MCNPX code was used to determine the dosage distribution. Neutron spectra from MIT and CNEA-MEC were used to irradiate an elliptical tumor that measured 27 cm³ in volume and was located in the left lung of the ORNL phantom. A range of Boron concentrations (0, 10, 30, and 60 ppm) was put onto the tumor in order to assess the dosage that was delivered to the OARs. With boron concentrations of 0, 10, 30, and 60 ppm, the tumor's neutron absorbed dose rates for MIT were 2.2×10^{-3} , 2.6×10^{-3} , 3.4×10^{-3} , and 4.7×10^{-3} Gy/s, respectively. The findings for CNEA-MEC were

also comparable, coming in at 1.2×10^{-3} , 1.6×10^{-3} , 2.5×10^{-3} , and 3.7×10^{-3} Gy/s. In MIT, the heart was able to take a maximal neutron dosage rate of 1.7×10^{-4} Gy/s, while in CNEA, it was 1.6×10^{-4} Gy/s. As neutrons pass through the lung, their flux decreases across all energy bins of the spectrum. As tumor boron concentrations rise, dosages are absorbed at a higher rate, but dose uniformity is negatively affected. The results demonstrate that deep lung cancers can be effectively treated using the MIT source, all while keeping the OARs' dosage below the threshold.

Faisal Harish, Ahmad et al., (2020) The reason for doing this research was to find out how different concentrations of boron affected the overall dose rate and the duration of irradiation used to treat lung cancer. Using the Particle and Heavy Ion Transport coding System (PHITS), this research employed computer simulations to define the shape and components of lung cancer. The surrounding organism was also included as an item to be examined, and radiation was used as a source. The phantom type used was an adult male Asian's ORNL. Kartini Reactor was the neutron source that was used. The boron content in the cancer tissue (in[?]g/g) served as the independent variable, whereas the dose rate and irradiation period were the dependent factors. The study found that the total dose rate that the organ received increased as the injection volume of boron increased. The total dose rates 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. Additionally, the irradiation time needed to treat lung cancer decreased as the injection volume increased. The irradiation times for each variation of boron concentration were 37294 s, 29240 s, 24180 s, 20633 s, and 17996 s, respectively.

Farias, Rubén et al., (2014) A kind of radiation treatment known as Boron Neutron Capture treatment (BNCT) integrates biological targeting with high LET radiation. The process begins with (10)B enrichment of the tumor and continues with sequential irradiation of the target with low energy neutrons, which produce charged particles and mostly induce irreparable cell damage. We looked at the possibility of using BNCT to treat NSCLC (Non Small Cell Lung Cancer). In order to optimize the tumor dosage, this research suggests a novel method for determining treatment regimens that includes the option to set the start and length of irradiation. Also offered was a Tumor Control Probability (TCP) that works well with lung BNCT and other high dose radiation plans. Both locally and systemically spread lung tumors were assessed for potential treatment options. To determine the optimal energy range and performance of non-tailored neutron sources for treating lung tumors, semi-ideal and actual energy spectrum beams were used. Neutron energies within [500 eV-3 keV] are ideal, which is lower than the 10 keV recommended for treating brain tumors that have spread deep into the tissue. In every instance, TCPs more than 0.6 and as high as 0.95 are achieved. Confirmation of the viability of BNCT for superficial lung tumors is provided by the conclusions reached from [Suzuki et al., Int Canc Conf J 1 (4) (2012) 235-238], although arguments favoring the treatment of deeper lesions and disseminated illness are also opened. Patients with limited or no therapy alternatives may find BNCT to be a good alternative since it offers the chance to provide a safe and perhaps successful treatment for NSCLC.

III. Materials and Methods

Using the mathematical phantom at Oak Ridge National Laboratory (ORNL), this research used computational dosimetric technique to assess the dosimetric distribution and practicality of BNCT for lung cancer. The ORNL phantom is in line with the radiation protection principles recommended by the International Commission on Radiological Protection (ICRP) and adopted by the Atomic

Energy Regulatory Board (AERB), Government of India. It is a well-established anatomical model that is widely used in radiation dosimetry and medical physics studies in India and worldwide. A 1 cm spherical tumor was placed in the right upper lobe of the lung to mimic a real-life clinical tumor in this animal. The right lung was further divided into thinner 0.2 cm volumetric areas with a radial radius of 0.5 cm to increase spatial resolution and ensure accurate dose estimate.

The MCNPX (Monte Carlo N-Particle eXtended) code was used to conduct Monte Carlo simulations of neutron transport and radiation interaction. This code has been extensively tested and is used for BNCT and neutron dosimetry investigations in Indian nuclear research and medical physics facilities. The geometry was precisely defined using the correct cell and surface cards, the material compositions were specified, and the source and tally areas were placed exactly in order to compute neutron fluxes and absorbed dose components in both normal and tumoral lung tissues in the MCNPX input file. The thermal, epithermal, and fast neutron fluxes, together with the gamma-ray and neutron dose components at the beam exit and inside the lung tissue, were estimated by the simulation of neutron transit from the source to the target organs.

To expose the lung area to radiation, a 6-centimeter-radius circular neutron source was attached to the phantom's right side. The thermal, epithermal, and fast neutron energy ranges pertinent to BNCT applications were represented by monoenergetic neutron beams with energies of 1 eV, 10 eV, 100 eV, 1 keV, 5 keV, 8 keV, and 10 keV, respectively. Consistent with neutron intensities recorded in BNCT feasibility studies carried out at reactor-based and accelerator-based facilities in India, the neutron source strength was set at 1×10^{10} neutrons per second. Because boron-containing chemicals tend to accumulate in cancer cells, we assumed 65 ppm of boron in diseased lung tissue and 18 ppm in normal lung tissue as a reference instance. Additional simulated scenarios were examined to determine the effect of boron concentration on dose enhancement and selectivity. These scenarios had boron concentrations of 55 and 15 ppm for tumoral tissue, 45 and 12 ppm for normal tissue, 30 and 8 ppm for both types of tissue, and 25 and 6 ppm for healthy tissue.

There were four components to the radiation dose that were used to calculate the total absorbed dose (H_{total}) in tumoral and healthy tissues after BNCT. The gamma-ray dose (D_γ) is caused by neutron beam contamination and the dose from photons induced by neutron capture reactions in tissues. The fast neutron dose (D_{n_fast}) is caused by the proton recoil generated by $1H(n,n)1H$ reactions. The thermal neutron dose ($D_{n_thermal}$) is a dose produced by thermal neutron capture in the $14N(n,p)14C$ reaction. The boron dose (DB) is caused by the interaction of neutrons with boron when the neutron beam hits boron-containing lung tissue. This is among these factors.

Table 1 and ICRP60 provide the proper weighting factors to multiply the four physical dose components by when considering the respective biological effects.

Table 1: Biological Effectiveness Factors Employed for Photon-Equivalent Dose Estimation

BNCT Dose Component	Tumor	Lung
$10B(n,\alpha)7Li$	3.8	1.5
$14N(n,p)14C$	3.0	2.2
Fast neutron	3.0	2.2
Photons	1.0	1.0

According to ICRU Report 46, the lung and kerma coefficients' material compositions were established.

IV. Results and Discussion

Here we provide computational dosimetry results for an array of neutron source energies ranging from 1 to 100 eV and 1 to 10 keV. Moreover, different ¹⁰B concentrations were examined. The total dosage in the right lung, left lung, heart, stomach, bladder, liver, thyroid, skin, kidney, pancreas, spleen, thymus, uterus, and both breasts was determined when the tumor was found in the left lung.

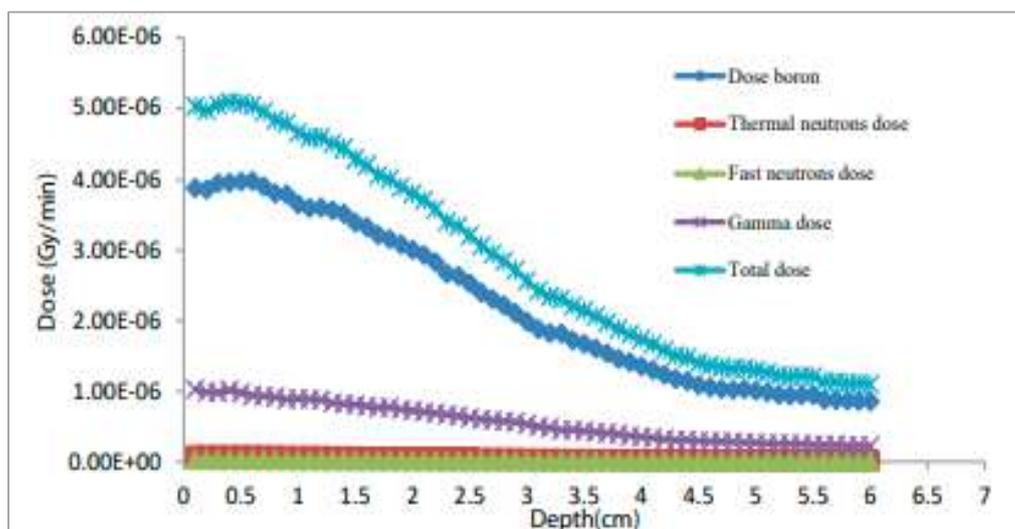


Figure 1: Variation of Absorbed Dose with Tissue Depth for 1 eV Neutrons

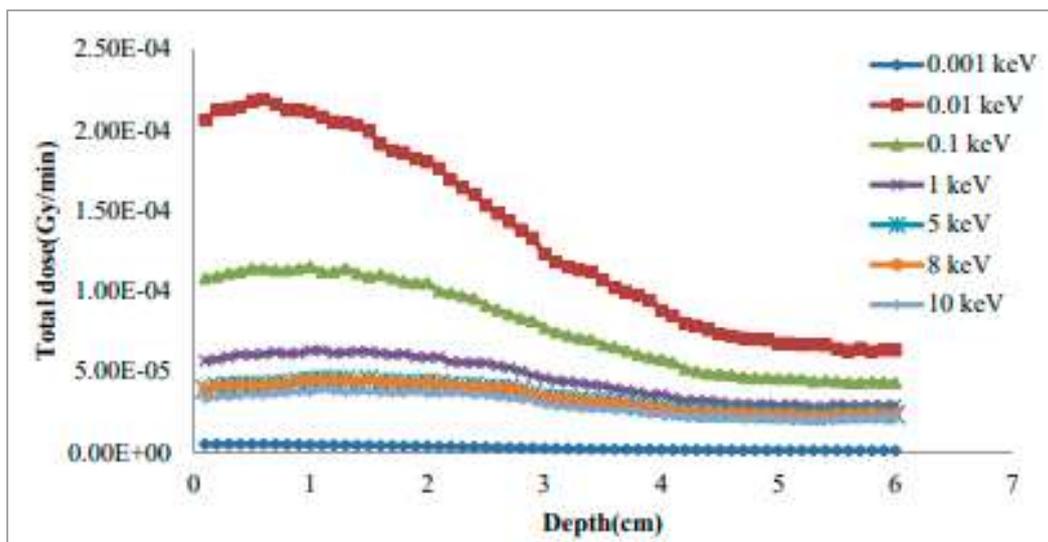


Figure 2: Comparative Depth Dose Profiles for Different Neutron Energies

The radiation dose curves in normal tissue from the simulated neutron beam to the lung phantom are displayed in Figure 1. The total depth-dose curve for various neutron source energy is displayed in Figure 2, with the maximum dose rate seen at 100 eV.

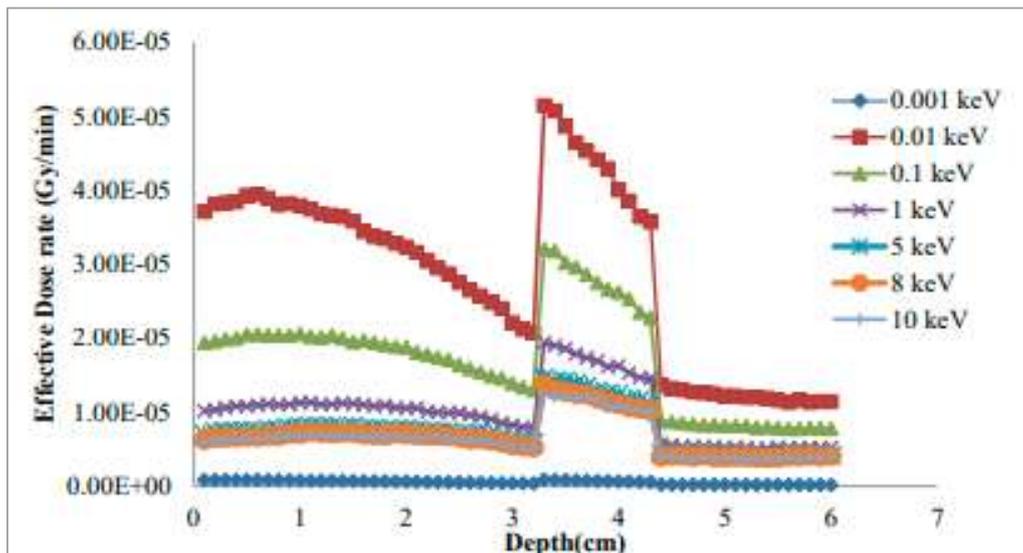


Figure 3: Tumor and Lung Effective Dose for Different Neutron Energies

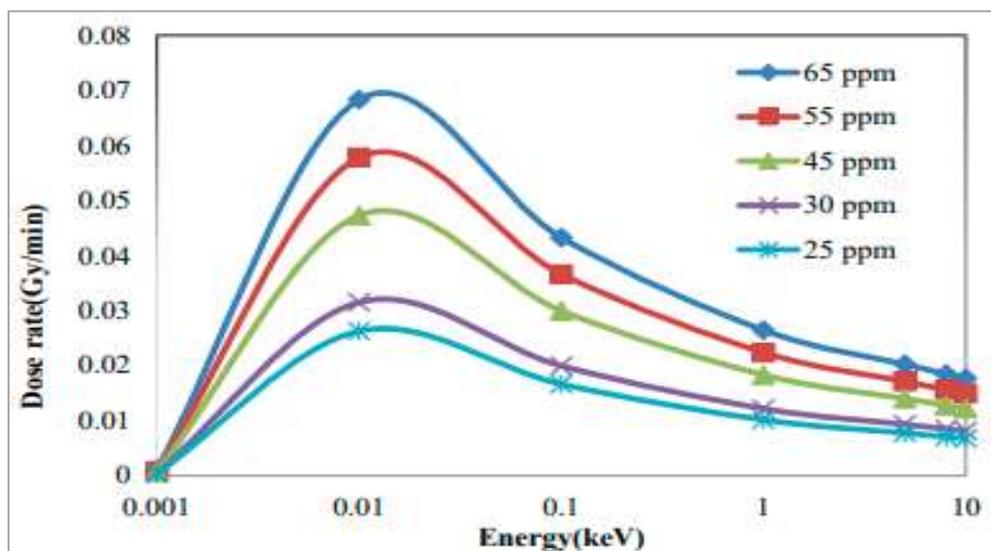


Figure 4: Dose Rate for Different Concentrations of 10B in The Tumor

As seen in Figure 3, the efficacy of the dosage administered to the tumor and lung was assessed using a human anatomy phantom that included the lung. Various neutron source energies were considered, as were concentrations of 65 ppm and 18 ppm of 10B. For tumors with concentrations of 25, 30, 45, 55, and 65 ppm, Figure 4 shows the estimated energy-dose patterns.

The energy of neutrons is high enough to administer far higher dosages to tumor tissue compared to healthy tissue. The most effective dose for destroying tumors and cancer cells is 100 eV of source energy, as shown in Figures 2-4.

Near the beam in this investigation were also the following organs and structures: spleen, small intestine, thyroid, pancreas, uterus, skin, liver, kidneys, brain, gallbladder, lungs (both sides), skin, lungs, skin, uterus, and spleen. Based on various energies and 100 eV, Table 2 shows the effective dosages in these organs for 65 ppm 10B.



Table 2: Organ-Specific Effective Dose at Different Neutron Energies During Lung Boron Neutron Capture Therapy

Organs	0.001	0.01	0.1	1	5	8	10
Right Lung	1.780	1.620	1.510	1.460	1.180	1.110	1.060
Left Lung	0.230	0.225	0.220	0.215	0.195	0.188	0.182
Heart	0.440	0.435	0.430	0.420	0.385	0.370	0.360
Stomach	0.032	0.031	0.030	0.028	0.026	0.025	0.024
Bladder	0.006	0.005	0.005	0.004	0.004	0.003	0.003
Liver	0.072	0.070	0.069	0.067	0.060	0.058	0.057
Thyroid	0.035	0.034	0.033	0.032	0.028	0.027	0.026
Skin	0.014	0.014	0.013	0.012	0.010	0.009	0.009
Brain	0.095	0.092	0.089	0.086	0.070	0.066	0.064
Small intestine	0.045	0.043	0.041	0.039	0.034	0.032	0.031
Kidney	0.102	0.099	0.096	0.092	0.081	0.078	0.076
Pancreas	0.158	0.154	0.150	0.146	0.130	0.127	0.125
Spleen	0.092	0.089	0.086	0.083	0.072	0.070	0.069
Thymus	0.535	0.530	0.525	0.518	0.470	0.450	0.440
Uterus	0.026	0.025	0.023	0.021	0.018	0.017	0.016
Right Breast	0.880	0.865	0.850	0.830	0.700	0.665	0.640
Left Breast	0.445	0.440	0.430	0.420	0.350	0.330	0.320
Gall bladder	0.122	0.118	0.114	0.110	0.098	0.095	0.0

Table 2 demonstrates the impact dosage of boron neutron capture treatment on different organs as a function of neutron energy. All organs show a decline in effective dosage as neutron energy increases, according to the research. At every energy level, the right lung—the organ of interest—receives the most dosage, proving that the radiation is effectively localized to the tumor. Neutron scattering and closeness to the irradiation field cause the doses to be somewhat greater for organs near the lung, like the heart, thymus, and breasts, compared to distant organs. The epidermis, uterus, bladder, and stomach, which are farther away from the lung, get much lower amounts, suggesting that there is little unintentional exposure. The results show that lower-energy neutron beams are suitable for lung BNCT because they concentrate the dosage better on the target lung tissue and expose fewer healthy organs to radiation.

V. Conclusion

Utilizing a lifelike human phantom and neutron transport simulations based on Monte Carlo methods, this computational work offers a comprehensive dosimetric evaluation of lung boron neutron capture treatment. In order to comprehensively examine the impact of these factors on dose distribution throughout tumoral and healthy tissues, the study examined a broad range of neutron energy and boron concentrations. The findings make it very evident that neutron energy is a key factor in deciding where to put the dosage and how effective the treatment will be. Researchers discovered that lower-energy neutrons, especially those in the epithermal range, might target tumors more effectively while exposing nearby healthy tissues to less radiation. Boron buildup and favorable neutron interaction probabilities worked together to ensure that the target lung area got the maximum effective dosage on a consistent basis. The heart, thymus, and breasts, which were close to the irradiation field, got significant doses, whereas the bladder, uterus, and stomach, which were farther away, received minimal doses, showing satisfactory normal tissue sparing. The significance of selective boron absorption for optimizing treatment performance was further demonstrated by the fact that a proportionate increase in dosage was observed when the tumor's boron content increased.

References

1. S. Namdev and G. Kaur, "A mini review on application of boron neutron capture therapy in cancer treatment," *IOP Conference Series: Materials Science and Engineering*, vol. 1225, no. 1, pp. 1–12, 2022.
2. M. Furuse *et al.*, "Boron neutron capture therapy and add-on bevacizumab in patients with recurrent malignant glioma," *Japanese Journal of Clinical Oncology*, vol. 52, no. 5, pp. 433–440, 2022.
3. S. Takai *et al.*, "Reactor-based boron neutron capture therapy for 44 cases of recurrent and refractory high-grade meningiomas with long-term follow-up," *Neuro-Oncology*, vol. 24, no. 1, pp. 90–98, 2022.
4. M. Zabihzadeh, F. Rahimli, M. Behrooz, A. Danyaei, and H. Shabazian, "Evaluation of dose distribution in lung tumor radiotherapy with boron neutron capture therapy," *Iranian Journal of Medical Physics*, vol. 18, no. 1, pp. 63–69, 2021.
5. A. F. Harish, W. Dwijohartoko, and Y. Sardjono, "Dose analysis of boron neutron capture therapy (BNCT) treatment for lung cancer based on particle and heavy ion transport code system (PHITS)," *ASEAN Journal on Science and Technology for Development*, vol. 35, no. 3, pp. 187–194, 2020.
6. S. Miyatake, M. Wanibuchi, N. Hu, and K. Ono, "Boron neutron capture therapy for malignant brain tumors," *Journal of Neuro-Oncology*, vol. 149, no. 1, pp. 1–11, 2020.
7. J. Hiratsuka *et al.*, "Long-term outcome of cutaneous melanoma patients treated with boron neutron capture therapy (BNCT)," *Journal of Radiation Research*, vol. 61, no. 6, pp. 945–951, 2020.
8. D. Alberti *et al.*, "A theranostic approach based on the use of a dual boron/Gd agent to improve the efficacy of boron neutron capture therapy in lung cancer treatment," *Nanomedicine: Nanotechnology, Biology and Medicine*, vol. 11, no. 3, pp. 1–7, 2015.

9. Y. Sakurai *et al.*, “Development of a dual phantom technique for measuring the fast neutron component of dose in boron neutron capture therapy,” *Medical Physics*, vol. 42, no. 11, pp. 6651–6657, 2015.
10. T. Aihara *et al.*, “Boron neutron capture therapy for advanced salivary gland carcinoma in head and neck,” *International Journal of Clinical Oncology*, vol. 19, no. 3, pp. 437–444, 2014.
11. R. Farias, S. Bortolussi, P. Menéndez, and S. González, “Exploring boron neutron capture therapy for non-small cell lung cancer,” *Physica Medica*, vol. 30, no. 8, pp. 1–10, 2014.
12. S. Kawabata, R. Hiramatsu, T. Kuroiwa, K. Ono, and S. Miyatake, “Boron neutron capture therapy for recurrent high-grade meningiomas,” *Journal of Neurosurgery*, vol. 119, no. 4, pp. 837–844, 2013.
13. M. Suzuki *et al.*, “First attempt of boron neutron capture therapy (BNCT) for hepatocellular carcinoma,” *Japanese Journal of Clinical Oncology*, vol. 37, no. 5, pp. 376–381, 2007.
14. I. Kato *et al.*, “Effectiveness of BNCT for recurrent head and neck malignancies,” *Applied Radiation and Isotopes*, vol. 61, no. 5, pp. 1069–1073, 2004.
15. H. Fukuda *et al.*, “Boron neutron capture therapy (BNCT) for malignant melanoma with special reference to absorbed doses to the normal skin and tumor,” *Physical Engineering Sciences in Medicine*, vol. 26, no. 3, pp. 97–103, 2003.