Jurnal Teknologi Reaktor Nuklir

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Journal homepage: jurnal.batan.go.id/index.php/tridam

Dose Optimization on Liver Cancer Proton Therapy and Boron Neutron Capture Therapy Using Particle and Heavy Ions Transport Code System

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ARTICLE INFO

Article history:

Received: 9 January 2021
Received in revised form: 7 February 2021
Accepted: 8 February 2021

Keywords:

Liver Cancer
Proton Therapy
BNCT
Dose Optimization
PHITS

A B S T R A C T

Liver cancer was the third leading cause of death from cancer in 2020 with 830,180 deaths worldwide. Radiotherapy is a common treatment method for liver cancer. Technological advances presented proton therapy and boron neutron capture therapy (BNCT) as alternatives with a lower dose on healthy organs. The objective of this research is to get a good dose distribution with higher tumor dose and lower healthy organ dose in proton therapy. A comparison with BNCT is done to get a better understanding of how both methods deliver the dose to treat the cancer while minimizing healthy organ doses. The research simulated proton therapy for cancer liver with Particle and Heavy Ions Transport Code System (PHITS), and a literature review for BNCT. The effectiveness of both methods were compared by tumor dose and liver dose. The optimal tumor dose for proton therapy is 86.01 Gy (W) with 0.67 Gy (W) liver dose. Proton therapy can replace conventional radiotherapy for tumors with complex shapes in dose delivery by utilizing its dose profile, while BNCT can give better tumor control on patients previously treated with conventional radiotherapy.

1. INTRODUCTION

Liver cancer has caused 830, 180 deaths worldwide in 2020, becoming the third in cancer-related deaths[1]. Currently, conventional methods for liver cancer treatment are surgery, radio wave ablation, ethanol injection, radiotherapy, and medications[2–5]. Advances in technology presented proton therapy and boron neutron capture therapy (BNCT) as alternatives to conventional radiotherapy. Proton therapy is an alternative treatment method for liver cancer treatment with a lower dose on healthy tissues[6, 7], averaging 30-50% lower dosage compared to IMRT[8]. In Indonesia, proton therapy is a new technology to treat cancer[9].

Latest dosimetry study for proton therapy was done by Ganjeh in 2019, focusing on dosimetry calculation of involved and non-involved organs in liver cancer proton therapy[10]. The research simulated proton therapy using a patient model with organs and a uniform beam model. Currently, there was no dosimetry calculation study of involved and non-involved organs for beam shape conforming to tumor in proton therapy. The objective of this research is to get a good dose distribution with higher tumor dose and lower healthy organ dose in proton therapy with a conformal beam shape. A comparison with BNCT is done to get a better

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DOI: 10.17146/tdm.2021.23.1.6183

understanding of how both methods deliver the dose to treat the cancer while minimizing the absorbed dose in healthy organ.

The research simulates proton therapy by using two beam models and a patient model. One beam model conformed to tumor shape, while the other follows the beam model of Ganjeh's study. The simulation is done in Particle and Heavy Ions Transport Code System (PHITS) software. The absorbed dose is calculated with an energy deposit tally for both beam shapes with an image and text output. The literature review references BNCT research with available tumor and liver dose data.

2. THEORY

Proton therapy utilizes the limited penetration of protons to deliver the prescribed dose to the target. Dose distribution of proton in matter follows the Bragg curve with a distinct peak, a low entrance dose, and a distal fall-off[6, 11]. Proton range in tissue generally follows its range in water, although a different calculation is required for organs with considerable density difference with water like bone and lungs[12]. Proton therapy uses a spread-out Bragg peak (SOBP) to distribute dose over the entire tumor. The benefits of this concentrated radiation dose include a higher tumor control level of hepatocellular carcinoma treatment[13] and the treatment availability for previously treated patients[14].

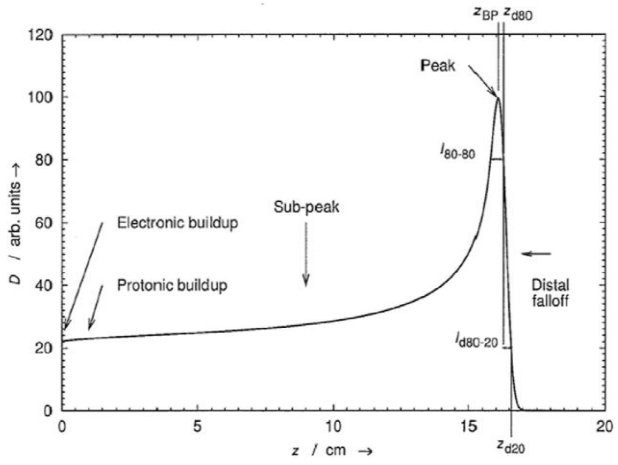

Fig. 1. Example of Bragg curve dose distribution. Source:[15]

Proton therapy has two different modalities to deliver dose to target volume: passive scattering beam and active scanning beam. Passive scattering utilizes a high-energy proton beam, using a range modulator to cover the tumor depth and a scattering nozzle to spread the dose profile. An aperture might be needed to match the tumor shape. Active scanning utilizes multiple monoenergetic proton beam, using an energy selector to filter proton energy and a set of scanning magnet to deliver dose to the target volume. The beam scans over slices of the tumor, depending on the target depth.

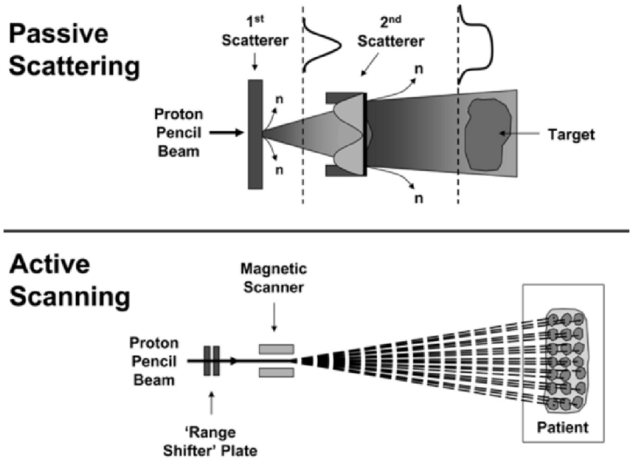

Fig. 2. Modalities of proton delivery in proton therapy. Source:[16]

Boron neutron capture therapy utilizes thermal neutron capture in boron-10 to induce fission. Boron is delivered to target cells using agents such as sodium borocaptate (BSH) and boronophenylalanine (BPA)[17]. Boron-infused cells irradiated by thermal neutron undergo fission to lithium-7 and helium-4, releasing 2.31 MeV in 5-9 μm range[18], localizing damage to boron-infused cells[19, 20]. Its effectivity depends on boron concentration in cancer cells compared to healthy cells, and various research on increasing boron concentration ratio has been done[21–23]. BNCT dose components consist of a high LET boron dose, intermediate LET nitrogen dose, and low LET gamma dose weighted in the photon-equivalent dose by their respective radiobiological effectiveness (RBE) and compound biological effectiveness (CBE) values[24].

In radiotherapy, dose fractionation prevents the side effects of radiation by giving healthy tissue time to repair itself[25]. The fractionation scheme used in this research follows the proton therapy protocol in Tsukuba University Hospital for hepatocellular carcinoma. The protocol specified 66 Gy RBE of proton dose is delivered in 10 fractions for tumor spaced more than 2 cm from both the intestinal tract and porta hepatis[26].

Minimizing radiation exposure is also done by delineating volumes to be treated. The concept of planning target volume (PTV), clinical target volume (CTV), and gross tumor volume (GTV) were used to minimize radiation exposure of organs at risk and reduce radiation effects on healthy tissues. GTV covers the whole visible tumor volume, CTV covers

suspected tumor area including GTV, and PTV covers irradiated area accounting for errors and movement of the organs. The organs at risk in this research are tissues in the proton's path: skin, ribs, and liver.

Particle and Heavy Ions Transport Code System (PHITS) is a program based on the Monte Carlo method to simulate particles and ions transportation. The software developed by JAEA in Japan can simulate particles with energies from 10^{-4} eV to 1 TeV/u. PHITS main applications are accelerator designs, radiotherapy planning, and radiation protection[27]. Physics libraries and nuclear models used in this research are ATIMA for ionization, INCL 4.6 for neutron and proton nuclear interactions, and EGS5 for photon interactions.

3. METHODOLOGY

The patient model uses the adult male geometry from Oak Ridge National Library – Medical Internal Radiation Dose and body composition from Report 89 of the International Commission on Radiological Protection. The simulation model includes the torso and the head sections with organs inside. The tumor model is a sphere with a 2 cm radius located inside the liver in -4 - 0 cm depth defined as the GTV. A sphere with a radius of 2.5 cm centered in the tumor was defined as CTV and a sphere with a radius of 3 cm centered in the tumor was defined as PTV. The tumor shape is constant for all treatment stages in the simulation. The beam modeled in this research is the gantry exit beam with a variable radius, depending on the modality. The uniform beam uses a similar radius for all energies, while the pencil beam differs for each.

The overall process of constructing the SOBP follows the methods used in proton therapy for liver cancer research by Ganjeh[10]. The SOBP construction starts by simulating the dose delivery of energies within 70 – 230 MeV using a 2 cm radius beam onto the patient model. The beam parameter references to parameters of the Proteus®ONE system by Ion Beams Application SA (IBA)[28]. Figure 3 shows dose peaks of 75 - 120 MeV protons occur inside the tumor model, thus become the optimum energies. The energies beyond 165 MeV peaks in the picture are outside the patient model.

Next, weights were assigned to each energy in the optimum range to construct the SOBP. Table 1 and Table 2 list the weights used for both beam models. The trial and error method gives energy weight to cover the entire tumor with an even dose. The highest weight was assigned to 118 MeV as the foundation for the SOBP. The beam model then uses the results to simulate proton therapy of the patient.

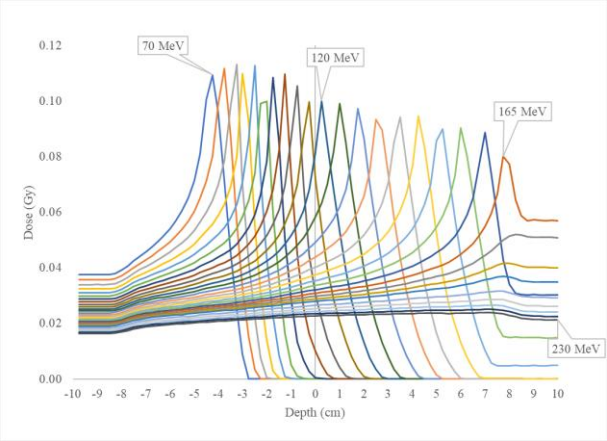

Fig. 3. Depth-dose simulation results for 70-230 MeV proton

Table 1. Energy weights in pencil beam model

Energy (MeV)	Weight	Energy (MeV)	Weight
118	13.7	96	2.3
116	4.6	94	1.2
114	4.4	92	1.6
112	3.9	90	1.9
110	2.3	87	1.6
108	2.8	84	1.2
106	2.3	82	1.2
104	2.3	80	1.2
102	2.3	77	1.2
99	2.3	75	1.2

Table 2. Energy weights in uniform beam model

Energy (MeV)	Weight	Energy (MeV)	Weight
118	2.208	96	0.268
116	1.204	94	0.268
114	1.137	92	0.268
112	0.803	90	0.234
110	0.602	88	0.201
108	0.602	86	0.201
106	0.401	84	0.201
104	0.468	82	0.201
102	0.401	80	0.201
100	0.334	78	0.201
98	0.334	76	0.201

The treatment simulation in PHITS uses 1 million particles and [T-Deposit] tally to calculate the dose in organs. The beam models use their respective weights and simulated in a single dose delivery from the front of the patient model. The RBE factors multiply each dose component of protons, neutrons, and photons to obtain Gy RBE. Proton uses 1.1[29], photon uses 1, and neutron

uses 20 for the RBE factor. Studies indicate the need for different proton RBE values for each patient[25, 30]. The total dose received by the patient is composed of the proton, photon, and neutron RBE doses expressed in Gy (W).

4. RESULTS AND DISCUSSION

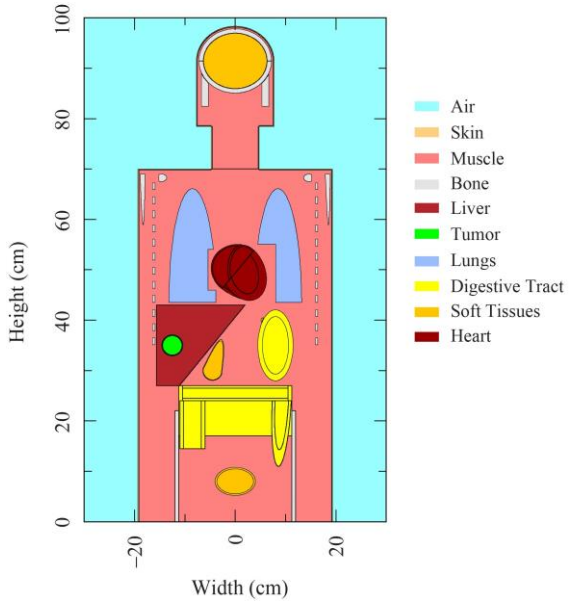

Fig. 4. Simulated front cross-section of the patient model

The doses received by organs at risk become a limiting factor in treatment planning. Each organ in the beam's path has a different dose threshold before any notable side effect appears. This limit varies from 2 Gy in the skin[31], 30 Gy in the liver[32], to 52 Gy in the bone[32]. Research result in Table 3 shows that each organ at risk received doses below the limit for each delivery. The lower doses delivered in each fraction prevents side effects and allows organs to heal.

Table 3. Dose in organ at risk

Organ	Pencil (Gy (W))		Uniform (Gy (W))		Dose Threshold (Gy (W))*
	Fx	Total	Fx	Total	
Skin	0.09	1.95	0.088	1.93	2
Ribs	0.2	4.04	0.182	4.01	52
Liver	1.25	25.09	1.39	30.77	30

*source:[31, 32]

The dose fractionation scheme splits the prescribed dose into ten deliveries. Each fraction in active scanning uses multiple mono-energy beams to reach a specific depth, while the passive scattering uses a range modulator. The uniform beam model uses multiple energy within a single beam to simulate the scattered protons. The pencil beam uses multiple mono-energy beams with various radius to simulate active scanning in different tumor depth.

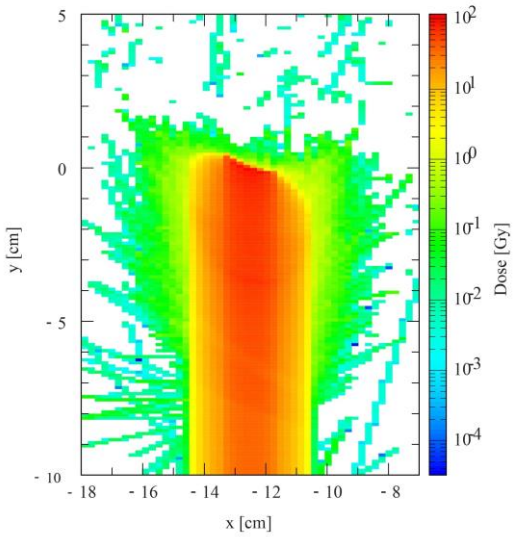

Fig. 5. Pencil beam dose profile

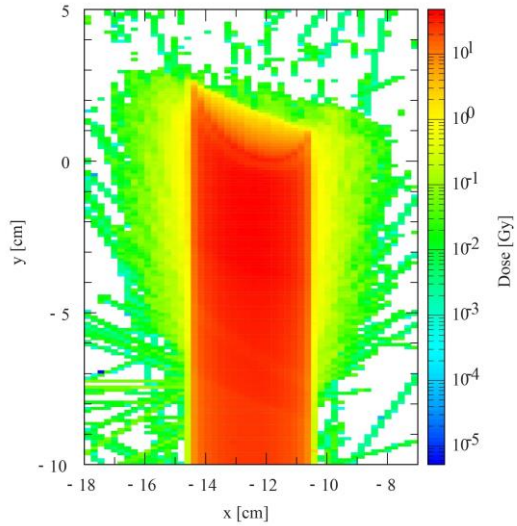

Fig. 6. Uniform beam dose profile

Figure 5 shows the pencil beam dose profile with visible dose gradient along the tumor's width. The varying radius of each energy created a dose gradient, with the highest dose in the center of the tumor shape. Figure 6 shows the uniform beam model with little to no dose gradient across the tumor width. The use of single beam radius allows similar absorbed dose on the beam path, a longer secondary particle range, and caused an increase in proton absorbed dose in the tissues within the beam trajectory. Both beam model ended with a concave shape because the differing tumor thickness along its width.

Table 4 and Table 5 listed the absorbed dose distribution in the organs and target volumes. Both beam model were able to achieve the target absorbed dose of 66 Gy (W) in GTV, but the pencil beam achieved a lower dose in healthy tissues due to its varying beam radius. The absorbed dose for the GTV, CTV, and PTV regions in pencil beam

are 86, 40, and 30 Gy (W) respectively, while the uniform beam gives 68, 51, and 40 Gy (W). Both beam models utilize a single entry point, so the healthy liver absorbed dose is smaller than the tumor absorbed dose and stays below the dose threshold. The dose in other organs were mainly composed of secondary particle from proton interaction with matter.

Table 4. Pencil beam organ dose

Region	Proton Dose (Gy RBE)	Photon Dose (Gy RBE)	Neutron Dose (Gy RBE)	Total Dose (Gy (W))
PTV	2.96×10^{1}	7.11×10^{-3}	2.60×10^{-1}	2.99×10^{1}
CTV	3.99×10^{1}	7.84×10^{-3}	2.75×10^{-1}	4.02×10^{1}
GTV	8.56×10^{1}	1.23×10^{-2}	4.35×10^{-1}	8.60×10^{1}
Liver	6.40×10^{-1}	9.62×10^{-4}	3.49×10^{-2}	6.76×10^{-1}
R Lung	8.69×10^{-8}	2.91×10^{-5}	4.82×10^{-4}	5.11×10^{-4}
L Lung	7.73×10^{-5}	1.20×10^{-4}	2.99×10^{-3}	3.19×10^{-3}
Stomach	4.68×10^{-5}	1.41×10^{-4}	2.08×10^{-3}	2.27×10^{-3}
Colon	5.30×10^{-5}	1.83×10^{-4}	3.04×10^{-3}	3.27×10^{-3}
Ribs	2.31×10^{-1}	2.27×10^{-4}	8.63×10^{-4}	2.32×10^{-1}
Kidneys	4.40×10^{-4}	1.57×10^{-4}	7.64×10^{-3}	8.24×10^{-3}
Pancreas	2.89×10^{-4}	1.24×10^{-3}	3.01×10^{-2}	3.16×10^{-2}
Adrenal	3.01×10^{-4}	1.42×10^{-4}	5.03×10^{-3}	5.48×10^{-3}
Gallbladder	2.93×10^{-4}	7.80×10^{-4}	1.70×10^{-2}	1.81×10^{-2}
Heart	1.20×10^{-4}	5.69×10^{-4}	9.05×10^{-3}	9.74×10^{-3}
Trunk	4.45×10^{-2}	8.66×10^{-5}	2.23×10^{-3}	4.68×10^{-2}

Table 5. Uniform beam organ dose

Region	Proton Dose (Gy RBE)	Photon Dose (Gy RBE)	Neutron Dose (Gy RBE)	Total Dose (Gy (W))
PTV	4.05×10^{1}	7.49×10^{-3}	2.65×10^{-1}	4.08×10^{1}
CTV	5.09×10^{1}	8.22×10^{-3}	2.84×10^{-1}	5.12×10^{1}
GTV	6.79×10^{1}	1.06×10^{-2}	3.74×10^{-1}	6.83×10^{1}
Liver	1.14×10	1.01×10^{-3}	3.63×10^{-2}	1.18×10
R Lung	6.56×10^{-6}	3.02×10^{-5}	4.15×10^{-4}	4.52×10^{-4}
L Lung	5.39×10^{-5}	1.18×10^{-4}	2.94×10^{-3}	3.11×10^{-3}
Stomach	1.20×10^{-5}	1.53×10^{-4}	1.76×10^{-3}	1.93×10^{-3}
Colon	5.49×10^{-5}	1.89×10^{-4}	3.51×10^{-3}	3.75×10^{-3}
Ribs	2.19×10^{-1}	2.27×10^{-4}	8.26×10^{-4}	2.20×10^{-1}
Kidneys	3.89×10^{-4}	1.76×10^{-4}	8.41×10^{-3}	8.97×10^{-3}
Pancreas	7.67×10^{-4}	1.44×10^{-3}	3.08×10^{-2}	3.30×10^{-2}
Adrenal	9.70×10^{-5}	1.38×10^{-4}	5.73×10^{-3}	5.96×10^{-3}
Gallbladder	2.54×10^{-4}	7.86×10^{-4}	1.87×10^{-2}	1.98×10^{-2}
Heart	9.28×10^{-5}	6.41×10^{-4}	9.08×10^{-3}	9.81×10^{-3}
Trunk	4.53×10^{-2}	8.89×10^{-5}	2.27×10^{-3}	4.76×10^{-2}

There are two liver BNCT studies used as references for comparison with the research result, listed in Table 6. These studies shows that the tumor and liver boron concentration ratio affects the maximum achievable tumor dose, since the liver dose is a limiting factor in BNCT[33]. Sufficient boron absorption difference in the tumor and the liver creates a dose gradient, minimizing the absorbed dose on healthy tissues[34].

Table 6. BNCT studies results

Study	Tumor Dose (Gy (W))	Liver Dose (Gy (W))	Tumor-Liver Boron Concentration Ratio (ppm)
Yanagie	35	5	113.7 / 16.3
Ganjeh	58.375	12.5	48 / 8

Source:[33, 34]

A comparison between proton therapy and BNCT can be seen from each method's advantages. The BNCT treatment allows a large dose gradient between the tumor and healthy liver, allowing patients previously treated with conventional radiotherapy to undergo BNCT treatment[35]. The proton therapy advantage is its dose profile which has a lower entrance dose an a stop point, resulting in fewer irradiation field and no exit dose[36].

5. CONCLUSION

The use of proton therapy for liver cancer provides an alternative to those untreatable by conventional methods. The pencil beam dose shows that the optimum dose can be achieved by using the conformal beam shape. Both pencil and uniform beam dose profile shows that the energy beam radius influences the range of secondary particles. The optimal tumor dose in this study is 86.01 Gy (W) with a 0.67 Gy (W) liver dose in pencil beam model. The proton therapy can treat tumors with complex shapes by utilizing its dose profile, and BNCT can improve tumor control for recurrent tumors.

ACKNOWLEDGMENT

Acknowledgment is given to Department of Nuclear Engineering and Engineering Physics, Faculty of Engineering, Universitas Gadjah Mada and Centre for Science and Technology Accelerator, National Nuclear Energy Agency. This research is performed under sponsorship by Lembaga Pengelola Dana Pendidikan (LPDP) the Ministry of Finance 2020/2021.

AUTHOR CONTRIBUTION

Hafiz Fahrurrozi, Andang Widi Harto, Isman Mulyadi Triatmoko, Gede Sutrisna Wijaya, and Yohannes Sardjono are the main contributors in this research and under sponsorship by Lembaga Pengelola Dana Pendidikan (LPDP) Kementerian Keuangan 2020/2021. All other authors read and approved the final version of the paper.

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