A D-D/D-T Fusion Reaction Based Neutron Generator System for Liver Tumor BNCT

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Abstract-*Boron-neutron capture therapy (BNCT) is an experimental radiation treatment modality used for highly malignant tumor treatments. Prior to irradiation with low energetic neutrons, a ^{10}B compound is located selectively in the tumor cells. The effect of the treatment is based on the high LET radiation released in the $^{10}B(n,\alpha)^7Li$ reaction with thermal neutrons. BNCT has been used experimentally for brain tumor and melanoma treatments. Lately applications of other severe tumor type treatments have been introduced. Results have shown that liver tumors can also be treated by BNCT. At Lawrence Berkeley National Laboratory, various compact neutron generators based on D-D or D-T fusion reactions are being developed. The earlier theoretical studies of the D-D or D-T fusion reaction based neutron generators have shown that the optimal moderator and reflector configuration for brain tumor BNCT can be created. In this work, the applicability of 2.5 MeV neutrons for liver tumor BNCT application was studied. The optimal neutron energy for external liver treatments is not known. Neutron beams of different energies (1eV < E < 100 keV) were simulated and the dose distribution in the liver was calculated with the MCNP simulation code. In order to obtain the optimal neutron energy spectrum with the D-D neutrons, various moderator designs were performed using MCNP simulations. In this article the neutron spectrum and the optimized beam shaping assembly for liver tumor treatments is presented.*

I. INTRODUCTION

Boron-neutron capture therapy[1,2] (BNCT) is theoretically an ideal radiation treatment modality for malignant tumors. Prior to irradiation with low energetic neutrons, a ^{10}B compound is located selectively in the tumor cells. The effect of the treatment is based on the high LET radiation, α particles (2.3 MeV) and recoiling lithium-7 nuclei, released in the $^{10}B(n,\alpha)^7Li$ reaction in thermal (<0.5 eV) neutron energies. The products of the neutron capture reaction have a short range (<10 μm) so that the ionization energy released causes a locally high dose in the area of ^{10}B compound, which accumulates in the tumor cells.

In addition to the dominant dose component, the boron dose (D_B) released in the boron capture reaction, the BNCT dose contains unwanted doses released in several background reactions. This background exists equally in the tumor tissue and the surrounding healthy tissue and creates the limiting factor to the treatment. Thermal neutrons, required for the boron capture reaction, produce, in addition a nitrogen dose (D_N) through the nitrogen neutron capture reaction $^{14}N(n,p)^{14}C$. Thermal neutrons contribute also the main gamma dose (D_γ) through $^1H(n,\gamma)^2H$ capture reaction with the hydrogen in tissue. The most critical background, hydrogen dose (D_H) or "fast dose", is mainly due to the proton-recoil reactions of the higher neutron energies (>1 keV) in the tissue. Hydrogen dose is highly dependent on the neutron beam design. The biological effect of these dose components is widely studied in BNCT and the radiation type related RBE (relative biological effectiveness) factors and boron compound related compound biological effectiveness (CBE) factors are determined for epithermal BNCT neutron beams[3,4]. The RBE factors are: 3.2 for hydrogen dose (RBE_H) and nitrogen capture dose (RBE_N) and 1 for gamma dose (RBE_γ). The compound factor for the boron compound boronphenylalanine (BPA) for ^{10}B in tissue is 1.3 and for B^{10} in tumor 3.8. With these factors, total dose in gray-equivalent (Gy-eq) units can be determined according to equation:

$$D_{tot} = CBE_B \cdot D_B + RBE_N \cdot D_N + RBE_H \cdot D_H + RBE_\gamma \cdot D_\gamma \quad (1)$$

Because the values of the CBE and RBE factors are dependent on the specific neutron source, boron compound, boron concentration and used endpoint, calculation of the exact dose-equivalent is not possible with the above mentioned factors and remains to be determined for a specific situation. Factors mentioned here are used to compare doses of the different BNCT neutron beams.

BNCT has been used experimentally for highly malignant and therapeutically resistant brain tumor[5,6,7] and malignant melanoma treatments[8,9]. The liver is the

most common target of metastases from many primary tumors (e.g. colorectal cancer[10]). Primary and metastatic liver cancers are highly fatal especially after resection of multiple individual tumors[8,11]. The response rate for nonresectable hepatocellular carcinoma to traditional radiation treatment or chemotherapy is very poor. However, the results indicate that the total low energetic neutron irradiation of the whole liver with a ^{10}B compound could be way to destroy all the liver metastases[12].

Liver tumor BNCT is a quite new approach of neutron capture therapy and only a few research projects of the subject have been performed[13,14,15,16]. The first human patient treatment has performed in Pavia, Italy, in 2002[11]. The thermal reactor neutron irradiation was performed into the isolated liver with 6 to 14 adenocarcinoma metastases. The liver was irradiated inside the thermal neutron field of 4×10^{12} n/cm^2, where neutrons were coming from every direction. Also in brain tumor treatments used boron-10 carrier, BPA-fructose was injected in the patient before removing the liver. After removing the liver, it was possible to measure the boron concentration with a good approximation. The boron concentration of the healthy liver tissue was measured to be 8±1 ppm (mg/kg) and the tumor tissue 47±2 ppm, allowing concentration difference of ~6:1 between the tumor and healthy liver tissue. Because of the different response of the tumor and healthy tissue cells to radiation, with these boron concentrations, the boron dose attained in the tumor is ~7 times higher than that of the healthy liver. In this kind of treatment configuration, gamma dose and the recoil proton background to liver, as well as the patient dose, is reduced to a minimum.

At Lawrence Berkeley National Laboratory developed compact neutron generators are using a 2 MHz or a 13.56 MHz radio frequency (RF) discharge to produce the deuterium and/or tritium ions from the plasma. RF-discharge yields a high fraction of monoatomic ion species (D^+ for D-D and 50% of D^+ + 50% T^+ for D-T) in the ion beam. The ion beam is accelerated to energy of 100 keV or higher to impinge the beam on a titanium coated copper or aluminum target where 2.45 MeV D-D or 14.1 MeV D-T neutrons are generated through fusion reaction. These neutrons can be moderated to thermal or epithermal energies for various applications. The gamma component in these moderated neutron beams is purely caused by secondary reactions in the moderator and thus can be minimized with the appropriate material selection. The cross-section of the D-T reaction is about two orders of magnitude higher than that of D-D allowing ~ 100 times higher neutron yield. The earlier theoretical studies of the D-D or D-T fusion reaction based neutron generators have shown that the moderator and reflector configuration for brain tumor BNCT can be created[17]. With the D-T neutron generator, the absorbed tumor dose (~70 Gy-equivalent to 3 cm deep tumor or ~50 Gy-equivalent to 6 cm deep tumor) can be achieved with a treatment time of ~45 minutes.

For brain tumor BNCT treatments, several definitions for the useful neutron beam energy have been determined from 0.4 eV to 40 keV[18,19]. The liver is a much larger organ and the neutron beam energy needed for the liver treatments could vary from that of brain tumor treatments. The ideal neutron energy area for liver treatments was studied first in this work. Neutron beams of different energies (1eV < E < 100 keV) were simulated and the dose distribution in the liver model was calculated with the MCNP simulation code[20]. The main goal was to study the applicability of 2.45 MeV D-D and 14.1 MeV D-T neutrons for external liver tumor BNCT applications. In order to obtain the optimal neutron energy spectrum with the D-D and D-T neutrons, various moderator designs were performed using MCNP simulations. In this paper, the neutron spectrum and the optimized beam shaping assembly for liver tumor treatments is presented.

II. MATERIALS AND METHODS

First, the ideal neutron energy for sufficient penetration in the liver tissue in order to produce high ratio between tumor and tissue dose was determined. Next, neutrons from the D-D and D-T fusion reactions were moderated to close to optimal neutron energy spectra, and dose calculation in the liver model was repeated with these beams. The methodology used in the study is determined in this section.

I.A. Set up for a Study of the Ideal Neutron Energy

To find out the dose distribution in the liver with the different neutron energies, the MCNP simulations were carried out with the mono-directional neutron sources of energies (1eV < E < 100 keV). In this first part of the study, liver was modeled as a rectangular phantom having dimensions of 25 × 25 × 12 cm^3 and the liver material composition described in ICRU Report 46[21] with 10 ppm of ^{10}B. The neutron beam was of circular shape with 10 cm radius. Each dose component was calculated in small cylindrical tally volume cells along the neutron beam centerline (from 0.5 cm to 20 cm depth) in the liver model using ENDF-neutron kerma factors defined in the T2 database[22]. The RBE and CBE factors specified for brain tumor treatments were used as described in the introduction. Tumor to healthy tissue boron concentration ratio was assumed to be 6:1 as presented in the previous liver tumor treatment study[11]. The goal was to obtain high therapeutic gain (tumor dose/maximum tissue dose) in the area of liver (>2 cm depth) and especially at the deep points, the 6 and 8 cm depths.

I. B. Model of the Neutron Source and Beam Shaping Assembly

In this study, the neutron source model was tandem axial neutron generator. The area of the source cone was 250 cm^2 with an extraction area of 40 cm^2. A target of these dimensions can hold 25% DF or 150 kV voltage at 1 A current and 150 kW power, when the power density on the target is 600 W/cm^2. This source geometry allows increased neutron source brightness and leads to a higher neutron yield (for D-D operation, 1.2×10^{12} n/s instead of 10^{12} n/s). With the same parameters, ~10^{14} n/s D-T neutron yield can be obtained.

Moderator materials were chosen to be iron for the first stage of moderation and Fluental^{TM23} for the second stage of moderation. Iron was chosen because it has high inelastic scattering cross section above 860 keV and a window at 20 keV. It decreases the fast neutron flux in the range of 1 to 2.45 MeV. Fluental^{TM} is a mixture of 69% AlF_3, 30% of metallic aluminum and 1% of LiF. The material combination of Fluental^{TM} is ideal to decrease the high neutron flux in the range of >100 keV. With these moderator materials over-moderation can be avoided. The reflector material was chosen to be bismuth and the shielding material at the front face, lithiated polyethylene. The moderator was a cone-shaped structure. The shape of beam aperture was square with dimensions 25 × 25 cm^2. A beam delimiter of 10 cm thickness was used to direct neutrons forward in order to limit neutron scattering to the healthy tissue outside the liver area. The cross-section and the dimensions of the beam shaping assembly are shown in figure I (a) from the side and (b) from the top. The aim was to create neutron spectra of useful neutron energies found in the first part of this study.

I. C. Dose calculations with the D-D and D-T Source

A more accurate liver model was modified for dose calculation with moderated D-D and D-T fusion neutrons. This liver model was created assuming the average dimensions of the liver are 21-22.5 cm across its widest point, 15-17.5 cm at its greatest height and a depth of 10-12.5 cm from front to back. The shape of the liver was assumed to be 1/8 of an ellipsoid and with mass of 1900 g. The liver was placed in the trunk modeled to be rectangular shape with dimensions of 40 cm in height, 60 cm in width and 15 cm in depth. Figure I is showing the liver model from all three directions. The body tissue was described according to ICRU 33 adult soft tissue[24] and liver tissue according to

ICRU report 46, both with 6 ppm of ^{10}B. The trunk was placed at the 5 cm distance from the beam exit,

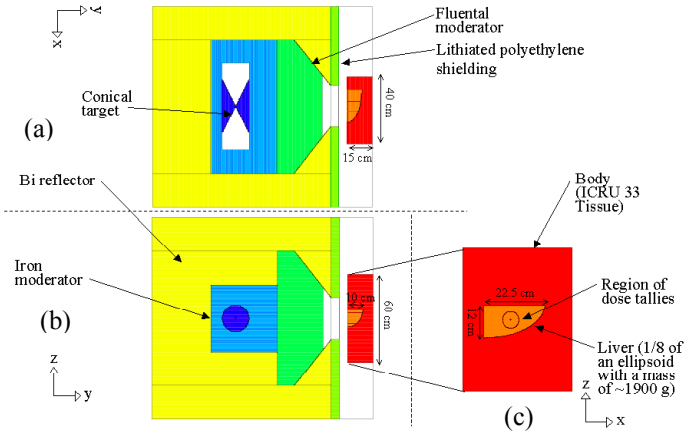

FIGURE I. Cross-section of the studied beam shaping assembly, liver phantom and the neutron source (a) from the side and (b) from the top and just the liver phantom from the beam direction (c).

because in reality it would be hard to place a patient closer to the wall and the beam exit. However, the distance between the beam exit and the patient should be reduced to a minimum to avoid unwanted neutron scattering from the beam to the healthy tissue area.

The dose calculation was performed at the beam central axis, as with the first liver model described in section I.A. The maximum healthy tissue dose was limited to 15 Gy-eq, but the cases with 12 and 10 Gy-eq maximum dose were also considered. The liver was first modeled to be at the surface of the trunk, but in reality is located at least 2 cm deeper. For that reason, the location of the liver was assumed to be from 2 cm to 6.5 cm depth.

I. D. Figures-of-Merit

The deepest depth of the liver is the hardest to treat. For that reason, the 6.5 cm point (from the surface) was considered most critical. The figures of merit were the minimum treatment time and the therapeutic gain at the 6.5 cm depth in the liver model. The treatment time was described for three cases with maximum healthy tissue dose of 10 and 15 Gy-eq. Therapeutic gain was described to be the ratio of the tumor dose at the 6.5 cm depth and the maximum healthy tissue dose ($D_{8.5cm\text{-}tumor}/D_{max\text{-}tissue}$). The dose at the skin and the healthy tissue until depth of 2 cm should be minimized and thus more penetrating neutron beam was favored.

Table I. Therapeutic gain at the depths of 2, 6 and 8 cm with the mono-directional neutron beam in the liver phantom.

Neutron beam energy [keV]	Therapeutic gain ($D_{tumor}/D_{tissue\ at\ maximum}$)		
	At 2 cm	At 6 cm	At 8 cm
1 keV	5.55	2.59	1.54
5 keV	5.23	2.73	1.70
8 keV	5.06	2.70	1.71
10 keV	5.06	3.15	1.69
15 keV	4.16	2.30	1.47
20 keV	3.52	1.97	1.28
50 keV	2.02	1.11	0.77
100 keV	1.40	0.71	0.52

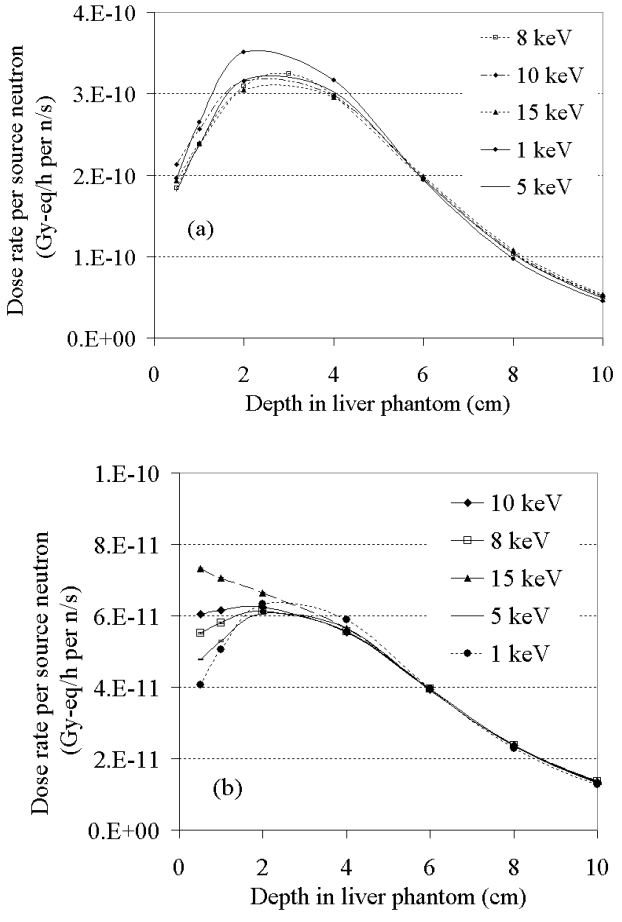

FIGURE II. (a) Total tumor dose profiles and (b) total tissue dose profiles with different neutron energies in the liver phantom. Dose units are Gy-eq per source neutron.

III. RESULTS

III. A. Liver Dose with the Monodirectional Neutron Sources with Energies 1 to 100 keV

The best therapeutic gain at the depth of 6 cm was attained with the 10 keV neutron source. With this source, the tumor dose maximum was located at the 2.5 cm depth and tissue dose maximum at the 2 cm depth. With 10 keV neutrons good therapeutic gain was also attained at 2 cm and 8 cm depths. Table I shows the therapeutic gains attained with all the studied neutron energies at 2, 6 and 8 cm depths. When maximum tissue dose was limited to 15 Gy-eq, the highest tumor dose at the 6 and 8 cm depths was reached with the 5, 8 and 10 keV neutron sources. In figure II (a) is shown the tissue depth dose and (b) tumor depth dose distribution in the liver phantom with the neutron energies $1 < E_n < 15$ keV. Energies higher than 15 keV caused similar tissue dose curve shape as 15 keV, where undesirably high skin dose was attained.

III. B. Liver Dose with D-D Neutron Source

The best four simulated moderators, material thickness and therapeutic gains at the deepest depth (6.5 cm) are shown in table II. Table II also shows the treatment times with the 10 Gy-eq and 15 Gy-eq maximum tissue dose limits. The highest therapeutic gain (2.02) was attained with moderator #2. The shortest treatment time was reached with moderator #1, when therapeutic gain remained slightly lower (1.98), because of the higher tissue dose. Total tumor dose maximum was located at the 2.5 cm depth in each case. In figure IV are shown the neutron energy spectra of moderator #2 (17 cm of Fe and 28 cm of Fluental™). Tumor and tissue depth dose curves with all the D-D moderators are shown in figure IV. In figure V (a) are shown important dose components with moderator #2. Neutron yield of the D-D source was assumed to be 1.2×10^{12} n/s in the dose calculations.

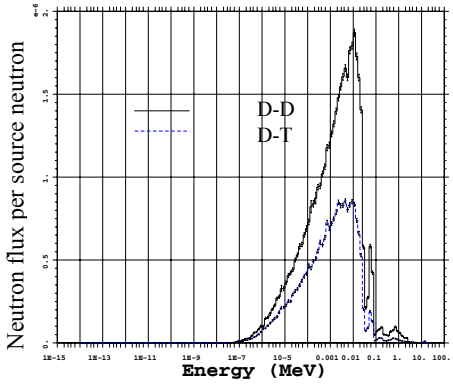

FIGURE III. Neutron energy spectra with the D-D moderator of 17 cm of Fe and 28 cm of Fluental™ and D-T moderator of 28 cm of Fe and 30 cm of Fluental™.

Table II. Material compositions and thicknesses of the simulated D-D and D-T neutron moderators, attained therapeutic gains and the treatment times with the maximum 10 Gy-eq and 15 Gy-eq tissue doses. Neutron yields of D-D and D-T sources were assumed to be respectively ~1.2×10^{12} and ~4×10^{13} n/s.

Moderator #	Fe thickness (cm)	Fluental thickness (cm)	Therapeutic gain at 6.5 cm	Treatment time and tumor dose at 6.5 cm			
				Maximum tissue dose 10 Gy-eq		Maximum tissue dose 15 Gy-eq	
D-D source of 1.2×10^{12} n/s				Time	Dose (Gy-eq)	Time	Dose (Gy-eq)
1	17	27	1.98	10.1 hrs	19.8	15.2 hrs	29.7
2	17	28	2.02	11.2 hrs	20.2	16.8 hrs	30.3
3	17	25	1.88	12.0 hrs	18.8	18.0 hrs	28.2
4	17	26	1.95	9.8 hrs	19.5	17.7 hrs	29.2
D-T source of ~4×10^{13} n/s							
5	27	30	2.40	45 min	25.3	69 min	38
6	27	32	2.38	43 min	23.8	65 min	35.7
7	27	35	2.15	113 min	22.7	170 min	34.1

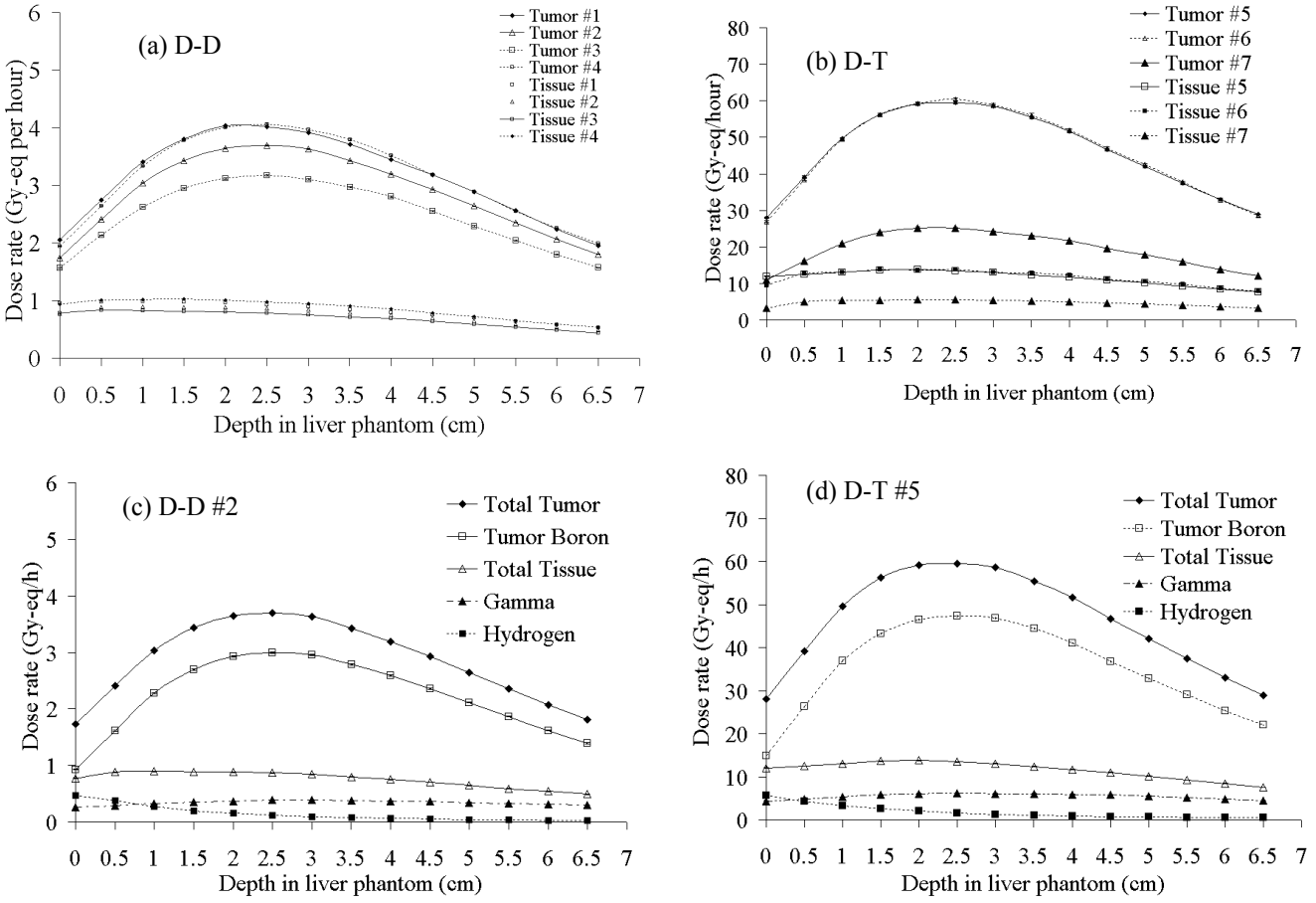

FIGURE IV. Total equivalent healthy tissue dose and tumor dose profiles in the liver phantom with the moderated D-D (a) and D-T neutron sources (b). Materials of moderator 1, 2, 4, 5, and 6 can be found in table II. In figure (c) is shown tissue and tumor depth dose distributions with the D-D moderator #2 and (d) D-T moderator #5. Neutron yield of 1.2×10^{12} n/s for D-D neutrons and 4×10^{13} n/s for D-T neutrons was assumed.

III. C. Liver Dose with the D-T Neutron Source

The best three simulated moderators, moderator material thicknesses and therapeutic gains at the deepest depth (6.5 cm) are shown in table II. Table II also shows also treatment time with 10 and 15 Gy-eq maximum tissue dose when D-T neutron yield of 4×10^{14} n/s is assumed. Highest therapeutic gain (2.4) and highest tumor dose at the deepest depth was attained with moderator #5 (28 cm of Fe and 30 cm of Fluental™). Moderator #6 gave shorter treatment time, because of the higher tissue dose and therapeutic gain as well as tumor dose remains lower. Neutron spectra with the best moderator (#5) is shown in figure III. Total tumor and tissue dose distributions with the D-T moderators are shown in figure V(b) and the dose components of the moderator #5 in figure V(d).

IV. CONCLUSIONS AND DISCUSSION

First part of this study showed, that neutron energies >15 keV are not very useful for liver BNC treatment, because they cause high tissue dose leading to smaller therapeutic gain. Best therapeutic gain at the deep depths (6 and 8 cm) can be reached with the 8-10 keV neutrons. In liver tumor case, when usually tumors may exist also in shallower depths, neutrons of all the lower energies 1keV < 10 keV are considered useful.

Results for D-D and D-T neutrons show that the 2.45 MeV and 14.1 MeV neutrons can be moderated to close to an ideal energy spectra peaking at 8-10 keV. With these moderators, good penetration of the D-T and D-D neutrons in the liver phantom and high therapeutic gain (>2) in the tumor until a depth of 6.5 cm is attained. Therapeutic gain for D-T neutrons was higher (2.40 versus 2.02), because the neutron spectra contain less unwanted fast neutrons. Fast neutrons in D-D neutron spectra cause high hydrogen dose background, which increases healthy tissue dose and leads to lower therapeutic gain.

With here presented D-D moderators, about 10 times higher neutron yield (~10^{13} n/s) is required to reduce the treatment time to an acceptable region of ~1 hour. However, therapeutic gain of the D-D neutrons could be increased with the different moderator, if it is possible to reduce the neutron flux at energies >10 keV. Two or more neutron beams could, as well, reduce the treatment time and needs to be studied next. Biological parameter that could reduce the treatment time is better boron compound uptake of the tumor cells and higher compound effectiveness in liver like some studies have indicated[25]. Another parameter that requires biological studies is determination of the biological effect (i.e. RBE and CBE factors) of D-D and D-T neutrons.

Next, here presented results will be verified with SERA treatment planning calculations with a liver model based on CT or MRI scans of patient. That way, liver dose distribution all over the liver and surrounding healthy tissue can be calculated more accurately and the optimal direction of one or more beams can be found.

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