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A single coned Poly-Biz moderator designed for animal irradiation in boron neutron capture therapy

Tatiana Sycheva [a,b], Evgenii Berendeev [a,b], Gleb Verkhovod [a,b], Sergey Taskaev [a,b,*]

[a] Budker Institute of Nuclear Physics, Novosibirsk, Russia
[b] Novosibirsk State University, Novosibirsk, Russia

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ABSTRACT

BNCT is considered to be a promising method for the treatment of malignant tumors, which ensures the selective destruction of malignant tumor cells by accumulating non-radioactive atomic boron-10 nuclei in them and subsequent irradiation with neutrons. As a result of the absorption of a neutron by boron, a nuclear reaction occurs with the release of energy in a cell containing boron, which leads to its death. To date, two drugs for targeted delivery of boron, boronophenylalanine and sodium borocaptate, have been developed, which ensures selective accumulation of boron in a number of tumors, and a number of charged particle accelerators with neutron-generating targets and with neutron beam shaping assemblies have been developed providing the quality of the neutron beam required for therapy. The paper presents a critical analysis of the methods used to form a therapeutic neutron beam and proposes a new concept of a neutron beam shaping assembly, supported by the results of numerical simulation validated by in-phantom measurements.

1. Introduction

1.1. Analysis of neutron beam shaping assemblies

Boron Neutron Capture Therapy (BNCT) is a form of binary radiotherapy that uses the uniquely high ability of the boron-10 atomic nucleus to absorb neutrons (Saurwein et al., 2012). As a result of neutron absorption by boron, a nuclear reaction $^{10}B(n,\alpha)^{7}Li$ occurs with a large release of energy in the cell, which leads to its death.

Ideally, a neutron source for BNCT should generate a monoenergetic neutron beam with an energy of ~10 keV (Yanch et al., 1991). Monoenergetic neutron beams with low particle energy are obtained for metrological purposes using the $^{7}Li(p,n)^{7}Be$ and $^{45}Sc(p,n)^{45}Ti$ reactions (Harano et al., 2010; Lacoste et al., 2010; Makarov and Taskaev, 2013). However, the intensity of these beams is insufficient for clinical BNCT applications. Therefore, for BNCT, neutron beams of the epithermal energy range with a maximum in the region of 10 keV are used for the treatment of deep-seated tumors or in the region of 10 eV for the treatment of superficial tumors. Since the energy of neutrons generated in the $^{7}Li(p,n)^{7}Be$ and $^{9}Be(p,n)^{9}B$ reactions is much higher than the required one, a neutron beam shaping assembly is used, which includes a moderator, reflector, absorber and filters (Minsky et al., 2013; Torres-Sánchez et al., 2021; Forton et al., 2009; Elshahat et al., 2007; Kononov et al., 2004; Palamara et al., 2002; Stichelbaut et al., 2006; Li et al., 2021; Lee et al., 2021; Bilalodin et al., 2019). Usually, magnesium fluoride is used as a moderator, since only fluorine has a noticeable cross section for inelastic neutron scattering in the neutron energy range below 1 MeV, and aluminum and iron to slow down neutrons with higher energy.

Of the projects implemented to date, the 30-MeV cyclotron with a beryllium target (Mitsumoto et al., 2010), 8 MeV linac with a beryllium target (Kobayashi et al., 2012) and 2.5 MeV accelerators of various types with lithium targets (Taskaev, 2015). The latter provide the generation of neutrons with the lowest energy – average 320 keV, maximum 780 keV, which makes it possible to form a therapeutic beam of epithermal neutrons that most meets the requirements of BNCT. In all projects with lithium target similar beam shaping assemblies with a magnesium fluoride moderator are used.

Previously, we analyzed neutron transport in a beam shaping assembly with magnesium fluoride moderator and found that protons with an energy of 2.3 MeV, and not 2.5 MeV are optimal (Zaidi et al., 2017, 2018). Of course, a decrease in the energy of protons entails a decrease in the yield of neutrons, but also noticeably decreases their energy, which makes it possible to use a moderator of a smaller thickness and, as

* Corresponding author. 11 Lavrentiev ave., 630090, Novosibirsk, Russia.
E-mail address: taskaev@inp.nsk.su (S. Taskaev).

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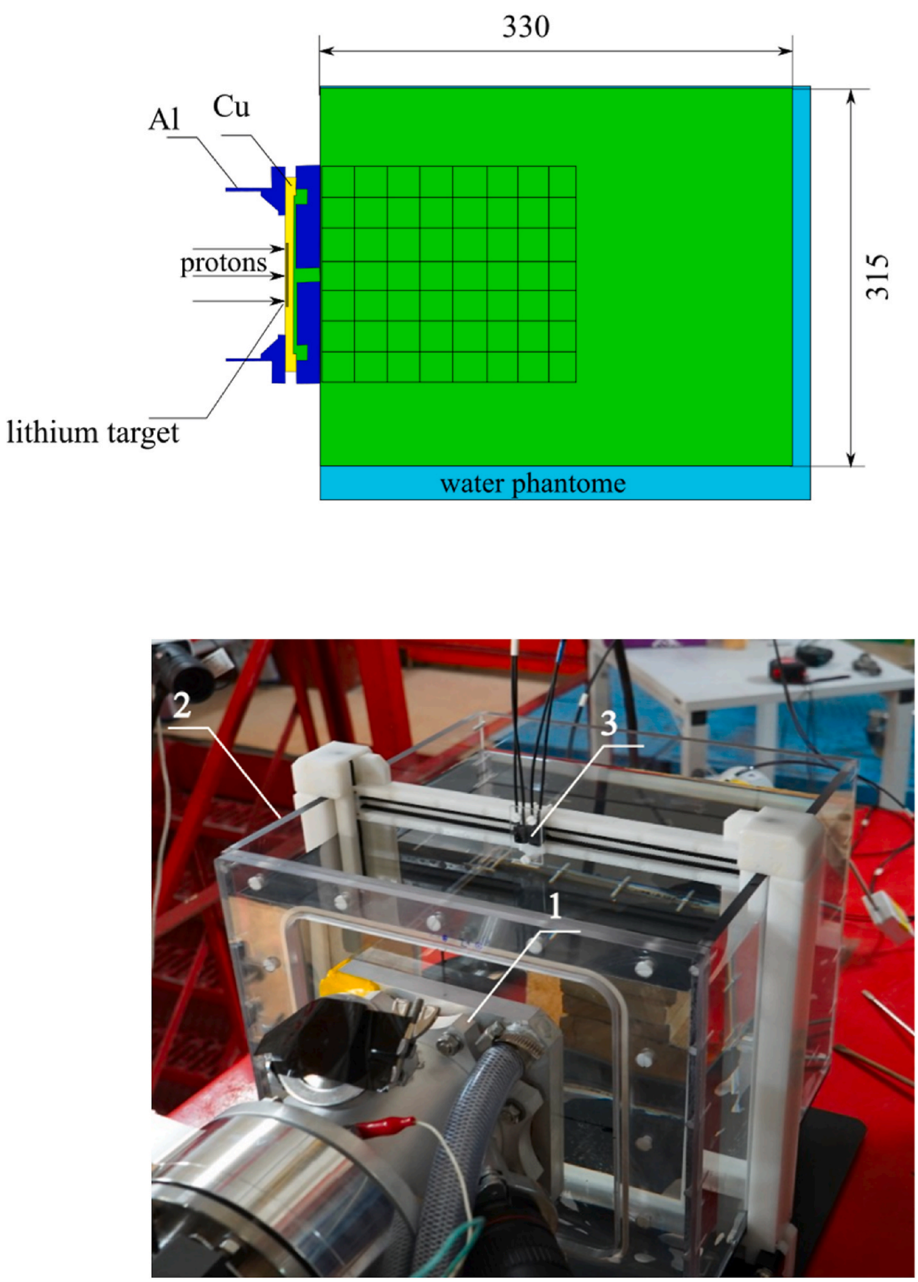

Fig. 1. Experiment scheme: 1 – lithium target, 2 – water phantom, 3 – detector of neutrons and γ-ray.

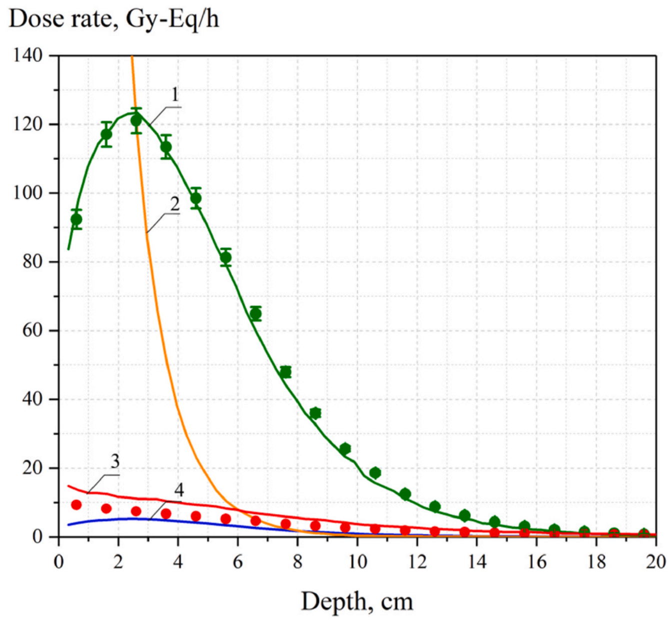

Fig. 2. Depth distribution of dose components in a water phantom along the axis of the proton beam at a proton energy of 2.1 MeV and a current of 1 mA: 1 – boron dose, 2 – fast neutron dose, 3 – γ-ray dose, 4 – nitrogen dose. Calculated values are shown as solid lines, measured as dots.

a result to obtain a neutron beam of even better quality without a loss in the flux density. Note that inelastic scattering of neutrons is no longer the governing process in their deceleration, as it was typical at higher energies. It is shown in (Torres-Sánchez et al., 2021) that a magnesium fluoride moderator provides the required quality of a neutron beam for BNCT at a proton energy of 2.1 MeV. Since at such a proton energy the average neutron energy is 100 keV, the process of inelastic neutron scattering is insignificant in neutron moderation.

This fact, as well as the results of our successful studies of the effect of neutron radiation on cell cultures, laboratory mice and pets (Kanygin et al., 2021, 2022) and new boron delivery drug testing (Popova et al., 2021; Vorobyeva et al., 2021) using a plexiglass moderator, forced us to question the necessity of using a magnesium fluoride moderator due to the noticeable cross section of inelastic neutron scattering. Let's consider another option – using a plexiglas moderator for BNCT.

2. Materials and methods

2.1. Experimental facility

Before describing the facility and the software used for the numerical simulation of neutron and γ-ray transport, let us define the concepts used about the components of the absorbed dose.

In BNCT, the total absorbed dose is the sum of four dose components with different relative biological effectiveness *RBE*: boron dose; the dose from the $^{14}N(n,p)^{14}C$ reaction (''nitrogen'' dose); fast neutron dose; and γ-ray dose. Before describing the proposed approach, we detail the processes leading to these four doses:

- Boron dose D_B: $^{10}B(n,\alpha\gamma)^7Li$ reaction produces two high-LET particles: ^4He and ^7Li.
- Nitrogen dose D_N: $^{14}N(n,p)^{14}C$ reaction produces high-LET proton.
- Fast neutron dose D_n: elastic scattering of neutrons by atomic nuclei of matter, mainly hydrogen, produces high-LET recoil nuclei, mainly protons.
- γ-ray dose D_γ: $^7Li(p,p'\gamma)^7Li$, $^{10}B(n,\alpha\gamma)^7Li$ reactions and ^7Be decay produces 478 keV photon, $^1H(n,\gamma)^2H$ reaction produces 2.2 MeV photon.

The total absorbed dose is equal to the sum of the dose components multiplied by the corresponding *RBE* or *CBE* (compound biological effectiveness) factor: $D_w = CBE{\cdot}D_B + RBE_p{\cdot}D_N + RBE_n{\cdot}D_n + RBE_\gamma{\cdot}D_\gamma$. *RBE* and *CBE* depend on many factors and their values vary among different authors. In the calculations, we use the values of the coefficients from the book (Saurwein et al., 2012): $CBE = 3.8$ for a tumor, $CBE = 1.3$ for healthy tissue, $RBE_p = 3.2$, $RBE_n = 3.2$, $RBE_\gamma = 1$.

The neutron and γ-ray transport is simulated by the Monte Carlo method using the NMC code (Yurov et al., 2012) and cross sections from the ENDF-VII database and from recent article (Taskaev et al., 2021a). The code implements a neutron source for protons with energies from 1.88 MeV to 2.5 MeV based on work (Lee et al., 1999).

It is desirable that the useful dose (boron dose) exceeds as much as possible the "harmful" dose equal to the sum of the three remaining doses: fast neutron dose, γ-ray dose, and nitrogen dose. The ratio of these doses, useful to harmful, we will call the therapeutic coefficient

$$TC = \frac{CBE \bullet D_B}{RBE_n \bullet D_n + RBE_\gamma \bullet D_\gamma + RBE_p \bullet D_N}.$$

As will be shown below, the introduction of such a simple coefficient turned out to be useful for analyzing the simulation results. At the same time, of course, it is necessary to determine such quantities as neutron fluxes of different energy ranges, photon flux, dose rates, advantage depth (depth in phantom at which the total therapeutic dose in tumor equals the maximum dose of the healthy tissue), advantage ratio (ratio of the total therapeutic dose in tumor to the total normal tissue dose over a given depth), treatable depth (depth at which the tumor dose falls below twice the maximum dose to normal tissue), treatment time (Saurwein et al., 2012; IAEA-TECDOC-1223, 2001).

We also propose to make one more improvement: use Poly-Biz (Poly-Biz specifications) – polyethylene with bismuth instead of plexiglass in the moderator. Bismuth in the form of a thin plate was used as a filter at the output of the neutron beam shaping assembly to reduce γ-ray dose. We propose to use it to reduce γ-ray dose not at the exit from the system, but volumetrically as part of the moderator.

We have considered three variants of beam shaping assemblies:

1) Optimal PMMA moderator (hydrogen atom density: 6 10^{22} cm^{-3}, oxygen atom density: 1.4 10^{22} cm^{-3}, carbon atom density: 4 10^{22} cm^{-3}, total density: 1.19 g/cm^3), surrounded by a graphite reflector with an outer diameter of 80 cm;
2) Optimal Poly-Biz moderator (hydrogen atom density: 5.39 10^{22} cm^{-3}, bismuth atom density: 6.6 10^{21} cm^{-3}, carbon atom density: 3 10^{22} cm^{-3}, total density: 2.92 g/cm^3), surrounded by a graphite reflector with an outer diameter of 80 cm (Fig. 6);
3) A beam shaping assembly, which we optimized earlier (Zaidi et al., 2017).

Experimental studies were carried out at the accelerator based neutron source with lithium target in the Budker Institute of Nuclear Physics (Taskaev et al., 2021b) to validate the evaluations.

Measurements of the spatial distribution of boron dose and γ-ray dose in a water phantom were carried out for the developed neutron and γ-ray detectors with cast polystyrene scintillators, one of which was enriched in boron, the other was not (Bykov et al., 2019, 2021). The detector was calibrated to the boron dose by measuring the boron concentration in the scintillator and assuming that tumor cells contained boron-10 at a concentration of 40 ppm. The detector was calibrated for the γ-ray dose by comparing the count rate of the detector with the readings of a γ-dosimeter DBG-S11D (wide range gamma area monitor DBG – S11D) placed in the maximum similar radiation field. A water phantom P3D01 was a vessel, the walls of which formed a parallelepiped

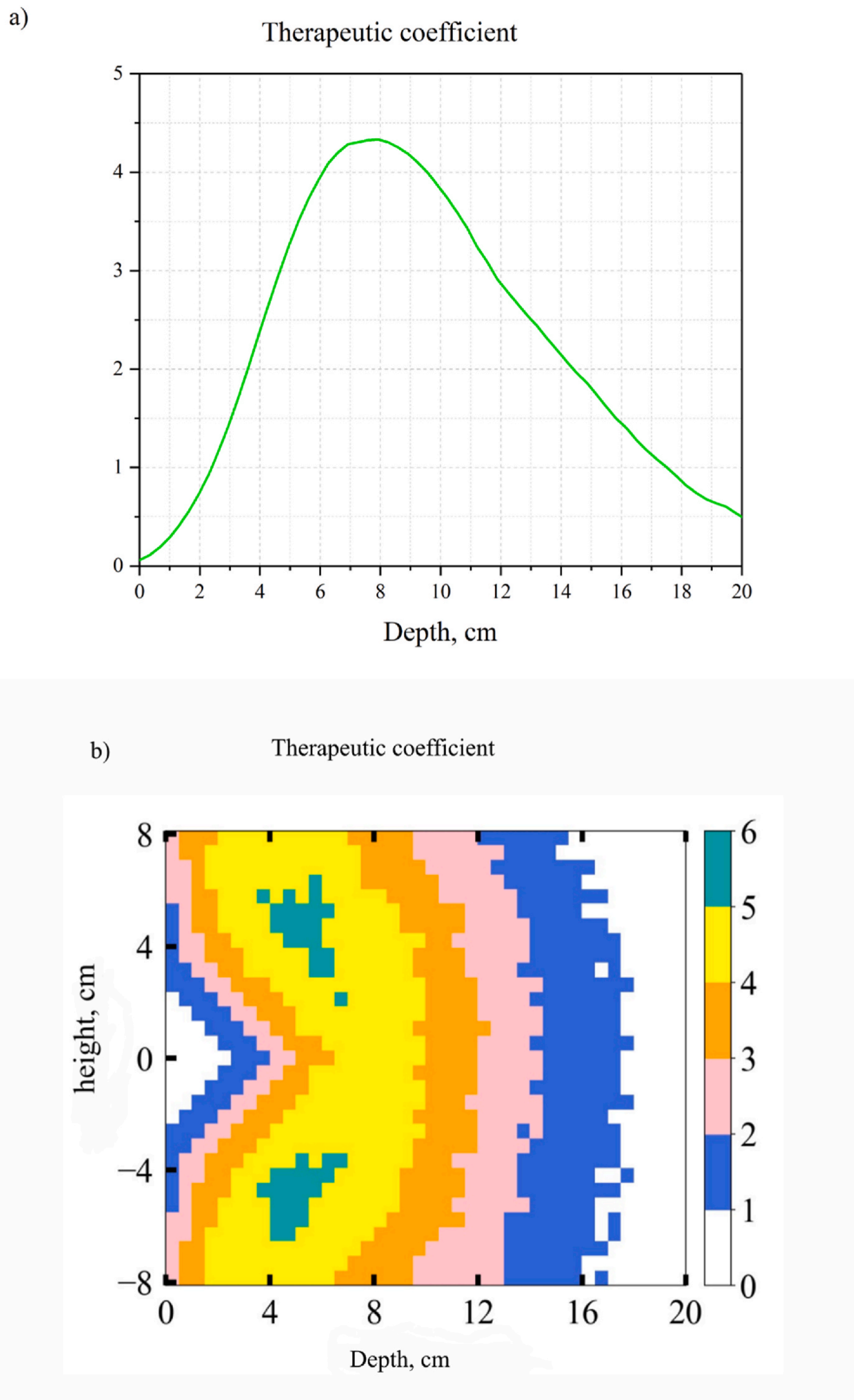

Fig. 3. Therapeutic coefficient a) depth distribution along the beam axis, b) two-dimensional distribution in the plane passing through the beam axis.

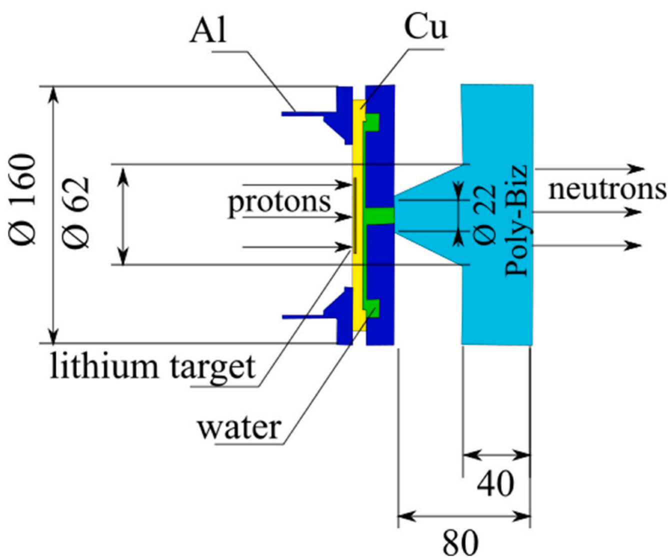

Fig. 4. The optimal shape of the moderator. The dimensions of the moderator are in mm.

with an internal space of 330 × 330 × 315 mm filled with water. The phantom walls were made of monolithic polycarbonate, their thickness was 8 mm. The back wall of the vessel was made of polyethylene terephthalate (PET) and had a thickness of 0.5 mm. A phantom with a thin wall was placed close to the lithium target as shown in Fig. 1. Neutron and γ-ray detectors were mounted on a carriage, which made it possible to move the detectors around the entire internal volume of the phantom.

3. Results and discussion

3D calculations of all four dose components were carried out on a rectangular grid with element volume 0.125 cm^3. Depth dose measurements by detectors were carried out along the central axis with a step of 1 cm, measurements by detectors in the orthogonal direction were carried out at depths of 2 cm.

The results of calculating the spatial distribution of all four dose components in the water phantom assuming a boron concentration of 40 ppm and the results of measuring the boron dose and the γ-ray dose are shown at Fig. 2. The deviation in boron dose is 10% and in γ-ray dose is about 40%. Statistical error in measurement is about 3%.

At a proton energy of 2.1 MeV, neutrons were emitted at 4 π, but had a dedicated forward direction. The mean neutron energy was 108 keV, the maximum 350 keV. Their fast thermalization occurred in water as a result of elastic scattering by atomic hydrogen nuclei. In Fig. 3 it can be seen that the dose rate of fast neutrons drops the fastest and from a depth of 6 cm it becomes less than the dose rate of γ-ray, which also drops with depth, but at a lower rate. The boron dose rate and the nitrogen dose rate first increase with depth due to the thermalization of neutrons, and then fall due to a decrease in the density of neutrons caused by their scattering.

Dependences of the therapeutic coefficient on the depth along the beam axis and its two-dimensional dependence are shown in Fig. 3. It can be seen that the therapeutic coefficient reaches the maximum value at a depth of 8 cm. For this reason, in numerous experiments with cell cultures and laboratory animals conducted at the experimental facility (Kanygin et al., 2021, 2022), a cylindrical plexiglass moderator with a thickness of 7.2 cm and a diameter of 20 cm was used. A moderator of this thickness significantly suppressed the dose of fast neutrons and ensures optimal irradiation quality.

Considering the two-dimensional distribution of the therapeutic coefficient, note that the therapeutic coefficient takes the maximum value not along the beam axis, but at a certain radius. This is due to the fact that the energy of the neutrons emitted forward is the highest. A thicker moderator should be used to approach the maximum therapeutic coefficient to the axis. The shape of such a moderator can be different, one of them, the optimal of several considered, is shown in Fig. 4. This is a combination of a truncated cone and a cylinder. The dimensions and angle are optimized to achieve a uniform radial distribution of the therapeutic coefficient.

A comparison of the therapeutic coefficient in a water phantom using cylindrical and optimal moderator is shown in Fig. 5. Here the moderator is placed between the target and the phantom without gaps.

A water phantom was placed close to the exit to each beam shaping assembly and depth dose calculations were carried out in it. The flux densities were calculated in the air at the output of the beam shaping assembly. The calculation results are presented in Table 1.

Analyzing the results, we find that the use of Poly-Biz instead of PMMA improves both the therapeutic coefficient and the boron dose rate. Therefor, the use of Poly-Biz instead of plexiglass improves the quality of the therapeutic neutron beam.

Now let us compare Poly-Biz with BSA with MgF_2 moderator. We see that at an energy of 2.05 MeV and below, the use of Poly-Biz also makes it possible to improve both the therapeutic coefficient and the boron dose rate, and the latter by a significant amount - more than twice (Fig. 7).

Comparing BSA with Poly-Biz and magnesium fluoride, we have to state that with their use it is possible to obtain the same quality of a neutron beam, if we look at the boron dose rate and the therapeutic coefficient, but the use of Poly-Biz makes it possible to obtain this even at a lower proton energy – 2.05 MeV instead of 2.3 MeV, and at a lower current - for example, 3 mA instead of 7 mA. Of course, experimental verification of these data is necessary.

The use of BSA with Poly-Biz allows the use of accelerators at lower energy, which improves the reliability of their operation, and reduces the therapy time by more than 2 times, which is also important for therapy. Also, the use of such BSA simplifies the requirements for a charged particle accelerator and this opens up both the possibility of optimizing the developed accelerators and the use of other accelerators that have not yet reached the required parameters.

Of course, this proposal requires experimental verification, which will be carried out after the manufacture of the BSA with Poly-Biz. Verification will involve not only experimental measurement by the developed diagnostic tools, but also a direct comparison with an already manufactured BSA with a moderator made of magnesium fluoride.

These two systems will be installed on an accelerator based neutron source and the parameters of the neutron beam will be measured by the same diagnostic tools, and this can be done simultaneously by placing one of the BSA in a horizontal path, and the other in a vertical.

4. Conclusion

The Vacuum Insulated Tandem accelerator had been developed in Budker Institute of Nuclear Physics. Neutrons were generated in ^{7}Li(p, n)^{7}Be reaction. A neutron beam shaping assembly was used for neutron slowing down, which includes a moderator, reflector, absorber and filters. Magnesium fluoride was considered to be optimal material for neutron slowing down because of noticeable cross section of inelastic neutron scattering. Previously, we showed that it was possible to use proton beam at an energy 2.3 MeV for neutron generation.

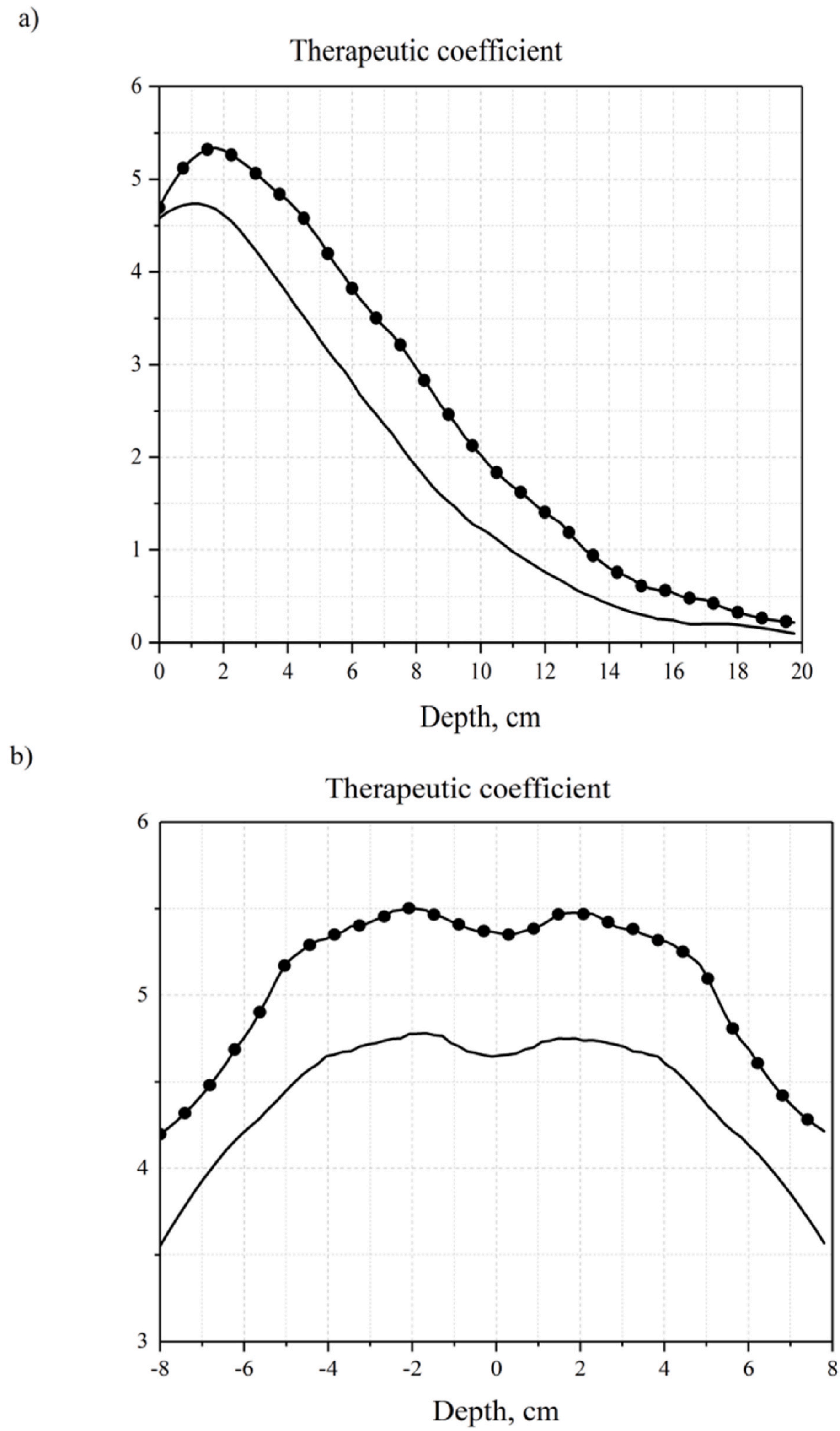

Fig. 5. Therapeutic coefficient for cylindrical and optimal moderator (•) a) depth distribution along the beam axis b) radial distribution at the depth 0.5 cm and 2 cm.

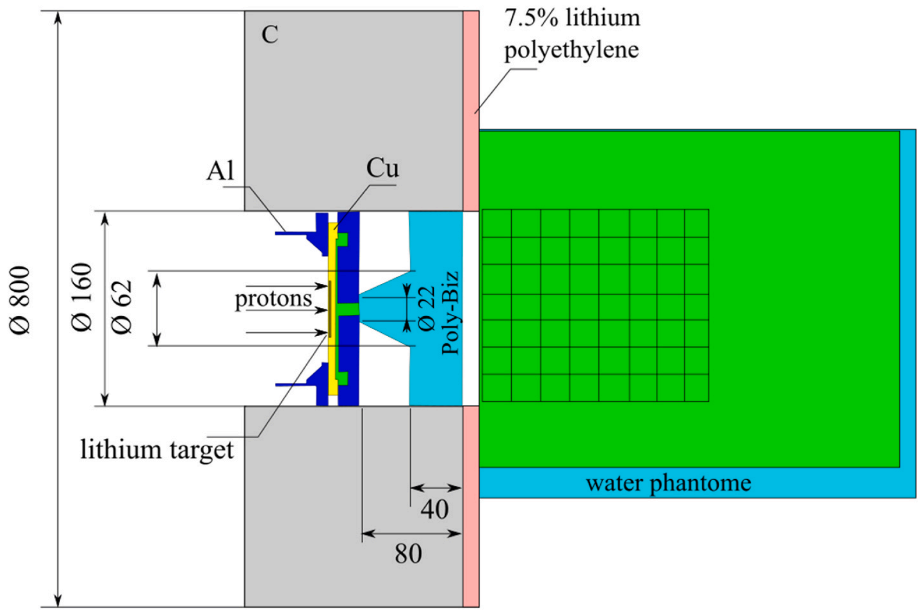

Fig. 6. Poly-Biz beam shaping assembly.

As a result of a critical analysis of our earlier decisions on the methods used to form a therapeutic neutron beam for boron neutron capture therapy and decisions of other research groups, as well as successful irradiation of cell cultures, laboratory animals and pets carried out at our experimental facility, we noticed that with the recent trend towards a decrease in proton energy the process of inelastic scattering in MgF_2 is no longer decisive in neutron moderation, and it was decided to consider materials based on plexiglass as a moderator material.

To analyze the simulation results, we introduced a new coefficient equal to the ratio of the useful dose (boron dose) to the "harmful" dose (sum of the fast neutron dose, γ-ray dose, and nitrogen dose). In this work we considered Poly-Biz as moderator material and get the neutron beam the same coefficient as with MgF_2 moderator and proton energy 2.3 MeV but at lower proton energy and current that could cause treatment time reducing and allowed more reliable neutron generation. Although the advantage depth of such a neutron beam is smaller due to the more thermal spectrum of neutrons, the applicability of the Poly-Biz moderator for the therapy of near-surface tumors and animals may be attractive.

Of course, this proposal requires experimental verification, which will be carried out after the manufacture of the BSA with Poly-Biz. Verification will involve not only experimental measurement by the developed diagnostic tools, but also a direct comparison with an already manufactured BSA with a moderator made of magnesium fluoride. Bismuth activation will also be studied.

Table 1
Calculation results for BSA with different moderators.

	Ep, MeV	BSA PMMA	BSA Poly-Biz	BSA MgF_2
Epithermal-neutron flux density, 10^7 cm^{-2}	2	2.85	3.24	
	2.05	4	4.53	
	2.1	5.07	5.7	
	2.3			5.8
Fast-neutron flux density,10^7 cm^{-2}	2	2.63	3.2	
	2.05	4.38	5.34	
	2.1	6.3	7.7	
	2.3			3.5
Thermal-neutron flux density,10^7 cm^{-2}	2	13.4	13.5	
	2.05	18	18.1	
	2.1	22.8	22.3	
	2.3			7.6
Photon flux density, 10^7 cM^{-2}	2	7.7	1.2	
	2.05	8.7	1.5	
	2.1	9.7	1.8	
	2.3			0.91
Maximum dose rate in tumor, Gy-Eq/h	2	27.33	27.98	
	2.05	37.78	38.80	
	2.1	48.86	50.94	
	2.3			16.8
Maximum dose rate in health tissue, Gy-Eq/h	2	7.2	7.1	
	2.05	10.1	10.6	
	2.1	13.6	14.1	
	2.3			4.7
Maximum boron dose rate, Gy-Eq/h	2	23.2	23.9	
	2.05	31.8	32.4	
	2.1	40.5	42.3	
	2.3			14
Maximum fast neutron dose rate, Gy-Eq/h	2	0.8	1	
	2.05	1.5	2.1	
	2.1	2.6	3.4	
	2.3			0.65
Maximum thermal neutron dose rate, Gy-Eq/h	2	1	1	
	2.05	1.4	1.4	
	2.1	1.8	1.8	
	2.3			0.6
Maximum photon dose rate, Gy-Eq/h	2	2.4	2	
	2.05	3.1	2.9	
	2.1	4	3.5	
	2.3			1.7
Therapeutic coefficient	2	5.70	6.20	
	2.05	5.42	5.89	
	2.1	5.35	5.77	
	2.3			5.8

CRediT authorship contribution statement

Tatiana Sycheva: Writing – original draft, Visualization, Validation. **Evgenii Berendeev:** Visualization, Software. **Gleb Verkhovod:** Investigation. **Sergey Taskaev:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

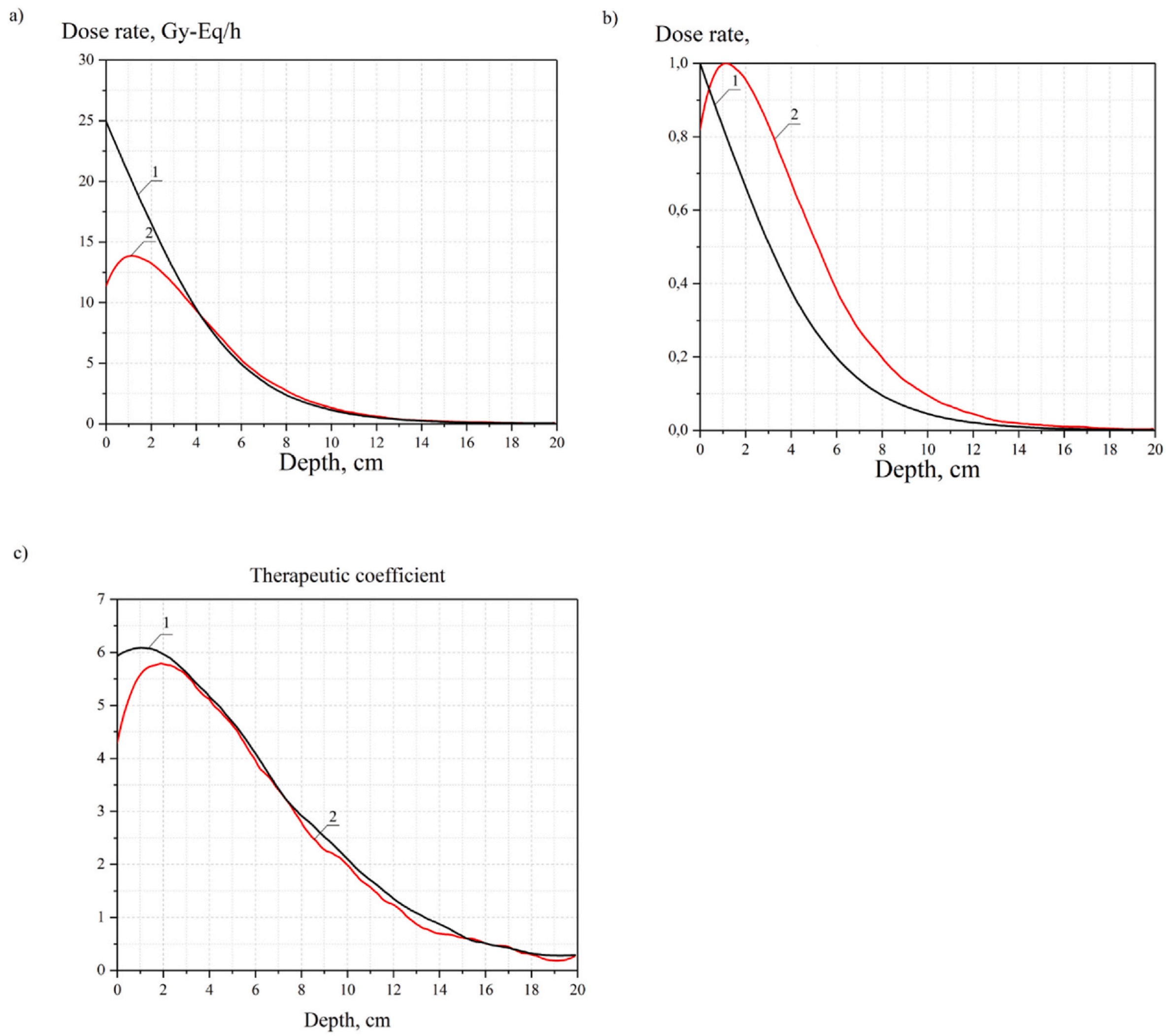

Fig. 7. Depth distribution for boron dose (a, b) and therapeutic coefficient (c) for BSA with Poly-Biz moderator and proton energy 2 MeV (1) and BSA with MgF_2 moderator (2) and proton energy 2.3 MeV.

Data availability

Data will be made available on request.

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