

Review

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Review

VITA Accelerator Neutron Sources: Status and Research Results

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Simple Summary

A new method of treating malignant tumors, boron neutron capture therapy (BNCT), is beginning to enter clinical practice. The aim of our study was to develop an accelerator neutron source for this therapy, as well as dosimetry tools and methods. We confirmed the compliance of the developed VITA facility with the presented recommendations, implemented the prompt γ -ray spectroscopy for boron imaging, and developed a set of techniques for measuring dose components. We were the first to implement lithium neutron capture therapy, which has advantages over BNCT. Thus, the VITA accelerator neutron source characterized by high efficiency, reliability and compactness, can be used for BNCT during which it is recommended to use the prompt γ -ray spectroscopy.

Abstract

Purpose: To develop an accelerator neutron source suitable for boron neutron capture therapy – a new promising method for treating malignant tumors, and to develop dosimetry tools and methods. **Methods:** Research into the transport and acceleration of a beam of charged particles, development and manufacture of an accelerator neutron source, and study of the radiation generated. **Results:** A facility called VITA has been created, which includes a tandem electrostatic accelerator of an original design for producing a 2.3 MeV 10 mA proton beam, a lithium target for generating neutrons in the ${}^7\text{Li}(p,n){}^7\text{Be}$ reaction, and a beam shaping assembly for forming a therapeutic neutron beam. Also, tools and methods for measuring the boron dose, γ -ray dose, and sum of the fast neutron dose and the nitrogen dose have been proposed and created. The conducted studies demonstrated the high efficiency of the VITA facility, the possibility of implementing the prompt γ -ray spectroscopy for boron imaging, the possibility of implementing lithium neutron capture therapy, which has advantages over BNCT, and also presented the results of the development of tools and methods for measuring the boron dose, γ -ray dose, and the sum of the fast neutron dose and the nitrogen dose. **Conclusion:** The authors strongly recommend using the prompt γ -ray spectroscopy in treatment, developing lithium neutron capture therapy, including in combination with BNCT, and note the high efficiency, reliability and compactness of the VITA facility.

Keywords: boron neutron capture therapy; neutron source; charged particle accelerator; neutron producing target; dosimetry; beam shaping assembly; boron delivery drug

1. Introduction

Boron neutron capture therapy (BNCT) is considered a promising method for treating malignant tumors [1,2]. Currently, several dozen accelerator neutron source projects are being implemented worldwide, with some of them being used for treatment or clinical trials [2,3].

The main objective of the research is to develop a compact accelerator neutron source that meets the requirements of BNCT. The proposed and developed VITA accelerator neutron source has become in demand for treatment and is actively used for scientific research into various aspects of BNCT.

2. Materials and Methods

The VITA accelerator neutron source is a facility that consists of a tandem electrostatic charged particle accelerator (Vacuum Insulated Tandem Accelerator, VITA), for producing a stationary monoenergetic proton or deuteron beam with an energy of 2.3 MeV and a current of 10 mA, a lithium target for producing neutrons in the ${}^7\text{Li}(p,n){}^7\text{Be}$ reaction, and a beam shaping assembly for producing an epithermal neutron beam [1] (p. 115-125), [2] (p. 255-260), [4].

BNCT requires neutron beams in the epithermal energy range, ideally in the range of 1 keV to 30 keV [5,6]. The best neutron-generating reaction is considered to be the ${}^7\text{Li}(p,n){}^7\text{Be}$ reaction due to the rapid increase in the reaction cross section near the reaction threshold (1.882 MeV) [5,7]. This allows the generation of a sufficient number of relatively low-energy neutrons (200-300 keV) at proton energies of 2.3-2.5 MeV [8]. Such neutrons can be slowed down to the required energy on a relatively thin moderator while maximally maintaining monoenergeticity. The use of a beryllium target, due to its smaller ${}^9\text{Be}(p,n){}^9\text{B}$ reaction cross section, requires a higher-energy proton beam. Consequently, the energy of the generated neutrons is higher, requiring a longer moderator, and the energy spectrum of the therapeutic neutron beam will be broader: there will be more undesirable fast neutrons and more undesirable thermal neutrons. The VITA facility was proposed for BNCT with the desire to implement the best solution, and this solution was successfully implemented.

At present, the VITA facility at the BINP site looks as shown in Figure 1. This facility makes it possible to obtain not only a proton beam, but also a deuteron beam, as well as to generate neutron flux of various energy ranges. The ion beam is characterized by high monochromaticity (0.1 %), the ability to change energy from 100 keV to 2.3 MeV and current from 0.5 mA to 10 mA. All this allows this facility to be used not only for BNCT, but also for other purposes; we will briefly list them at the end of the chapter.

The accelerator *1* consists of a cylindrical vacuum tank with a diameter of 1.4 m, a height of 2.3 m. The openings on the side are for the input and output of the ion beam, on the top – for vacuum pumping, and on the bottom – for connection to a high-voltage power supply. Inside the vacuum tank there are high-voltage and five intermediate cylindrical electrodes *1b*, which are located coaxially with the body of the vacuum tank. Frames for fastening diaphragms are welded into the electrodes on both sides and diaphragms with an aperture usually 20 mm in diameter are inserted in the negative ion acceleration path and in the high-voltage electrode and 30 mm in the positive ion acceleration path. The diaphragms are located along the diameter coaxially with the input and output flange of the ion beam input and output, and form an accelerating channel. A gas stripper *1c* is installed inside the high-voltage electrode coaxially with the accelerating channel, designed to convert negative ions into positive ones. The potential on the high-voltage and intermediate electrodes *1b* is supplied from the high-voltage power supply *1e* through a feedthrough insulator *1d*.

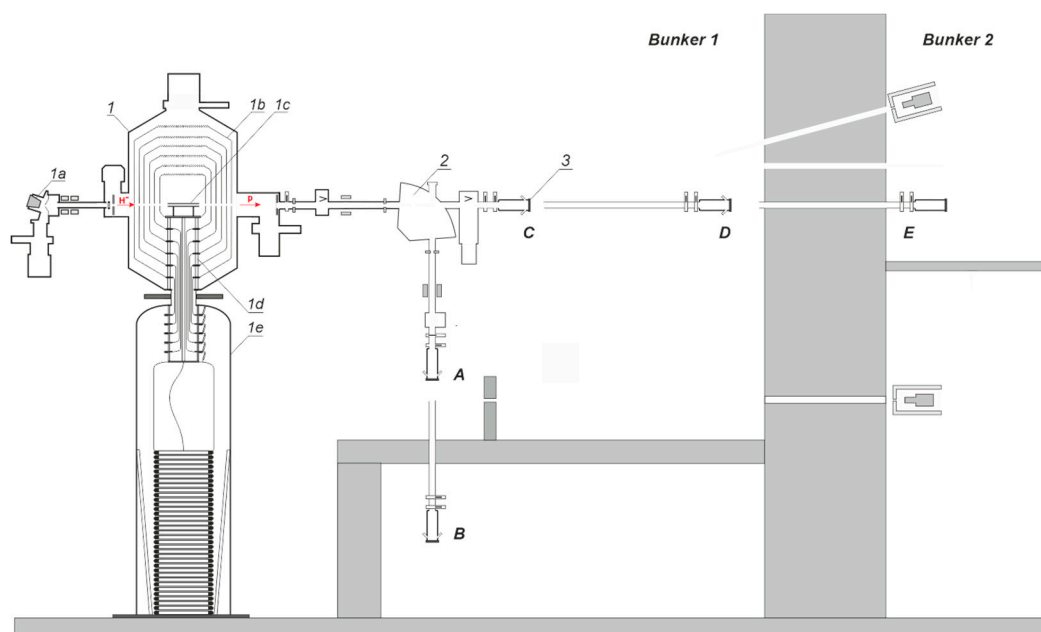


Figure 1. Layout of the VITA facility: 1 – vacuum insulated tandem accelerator (1a – negative ion source, 1b – intermediate and high-voltage electrodes, 1c – gas stripper, 1d – feedthrough insulator, 1e – high voltage power supply), 2 – bending magnet, 3 – lithium target. A, B, C, D, E – lithium target placement positions.

A beam of negative ions is obtained from a surface-plasma source 1a with a Penning geometry of the gas-discharge chamber. The beam is focused by a solenoid onto the accelerator input. The typical transverse size of the ion beam at a distance of 57 mm in front of the input of accelerator is 8–9 mm, the convergence is ± 30 mrad, the normalized emittance is from 0.13 mm mrad at a current of 0.5 mA to 0.2 mm mrad at a current of 3 mA.

This focusing of the ion beam at the accelerator's entrance aperture ensures a "hard" input beam. A highly divergent ion beam enters the accelerator, which is focused by the accelerator's strong electrostatic input lens into a beam 4–5 mm in diameter close to parallel. Negative ions are converted into positive ions in the gas stripper of the tandem accelerator. Then positive ions are accelerated by the electric field and, leaving the accelerator, are slightly defocused by the accelerator's output electrostatic lens. At a distance of 1.86 m from the accelerator center, the proton beam has a transverse size 10 ± 1 mm, angular divergence from ± 0.5 mrad to ± 1.2 mrad, and normalized emittance 0.2 mm mrad.

The lithium target 3 can be placed in one of five positions; in Figure 1, they are marked as A, B, C, D, and E positions. To direct the ion beam downward, a bending magnet 2 is used, which ensures the same focusing of the proton beam in the direction along and across the magnetic field.

The target units (3 in Figure 1) are made in the form of an aluminum tube with a diameter of 100 mm (Figure 2). Using a gate valve 1 with a standard CF100 connection, the unit is connected to the facility or to a specially designed lithium evaporation unit. For different applications, the target unit varies in length (from 131 mm to 443 mm) and the presence or absence of pipes for diagnostic equipment or observation windows located at an angle of 45° or 52.5° to the axis. A copper disk with a diameter of 144 mm and a thickness of 8 mm is sealed on the end of the target unit. On the proton beam side, a layer of lithium with a diameter of 92 mm and a thickness of 0.5 to 100 μm is applied to the copper disk using thermal evaporation in vacuum. On the reverse side of the copper disk, inside the diameter of 122 mm, four double-flow spiral channels are machined 3 mm deep and 6 mm wide, with a partition between the channels 1 mm thick for water cooling. A flat aluminum disk with a central hole for cooling water supply and two peripheral holes for water drainage is pressed against the reverse side of the copper disk. At a typical water flow rate of 17 l/min, turbulent water flow at a velocity of 4 m/s occurs in the cooling channels, ensuring efficient heat removal. It should be noted

that the lithium target is characterized by an extremely long service life due to its insensitivity to radiation blistering.

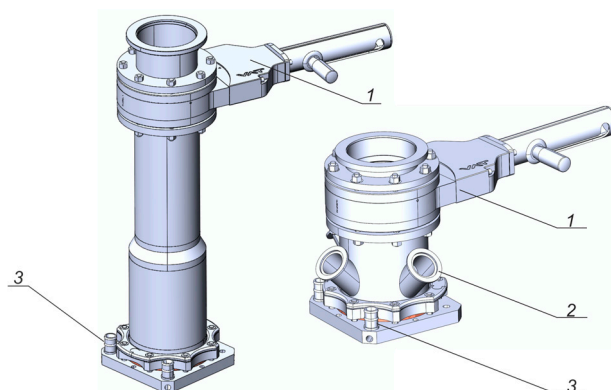


Figure 2. Target units: 1 – gate valve, 2 – pipes, 3 – cooling supply.

For scientific research on BNCT with cell cultures and laboratory animals, as well as for the treatment of pets with spontaneous tumors, the lithium target is placed in position A. The placement of a lithium target in position C is usually used to measure the parameters of the formed neutron beam in air and in a water phantom using developed diagnostic tools. The results of the conducted research are presented below in Chapter 3.

A lithium target is placed in position B to generate fast neutrons in the $\text{Li}(d,n)$ reaction for radiation testing of materials and equipment, including those developed for the International Thermonuclear Experimental Reactor ITER and the Large Hadron Collider at CERN. References to articles containing research results are provided in [9]. In the radiation-protected bunker, an additional room was made from concrete blocks with boron carbide with a wall and ceiling thickness of 46 cm to ensure an acceptable dose level in the control room.

The lithium target is placed in positions C or E when measuring the yield of particles in nuclear reactions and the cross section of nuclear reactions. To date, the cross-sections of 21 nuclear reactions have been measured, which are important for BNCT, the generation of a powerful flux of fast neutrons and neutron-free thermonuclear energy. References to articles containing results of measurements of nuclear reaction cross sections are provided in [9].

A lithium target is placed in position C to generate monoenergetic neutrons for the calibration of high-sensitivity two-phase cryogenic avalanche detectors designed to search for dark matter.

A lithium target is placed in position D to produce a thin beam of cold neutrons to confirm the solution obtained when solving the quantum problem of neutron motion in a $2(n+1)$ -pole magnet (Stern-Gerlach experiment).

Two next-generation VITA-II accelerator neutron sources have been developed for oncology clinics. Three modifications have been made to them. Firstly, the surface plasma source with the Penning geometry of the gas-discharge chamber developed by BINP was replaced by a D-Pace Filament Volume-Cusp Source [10]. Secondly, the negative hydrogen ion beam injected into the accelerator is additionally pre-accelerated by 100 keV. Thirdly, the sectional rectifier (high voltage power supply) was turned over and placed on the bottom of the feedthrough insulator, which made it possible to significantly reduce the facility height.

The VITA-II α facility was delivered to the BNCT Center at Xiamen Humanity Hospital (Xiamen, China), where clinical trials began on October 9, 2022. A photograph of the facility at the BINP site before being shipped to China is shown in Figure 3. The results of the first patient's treatment have been published [11].



Figure 3. The VITA-II α facility at the BINP site before being shipped to China.

The VITA-II β facility was delivered to the Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation (Moscow, Russia), where clinical trials will begin in April 2027. The scheme of the VITA-II β facility is shown in Figure 4.

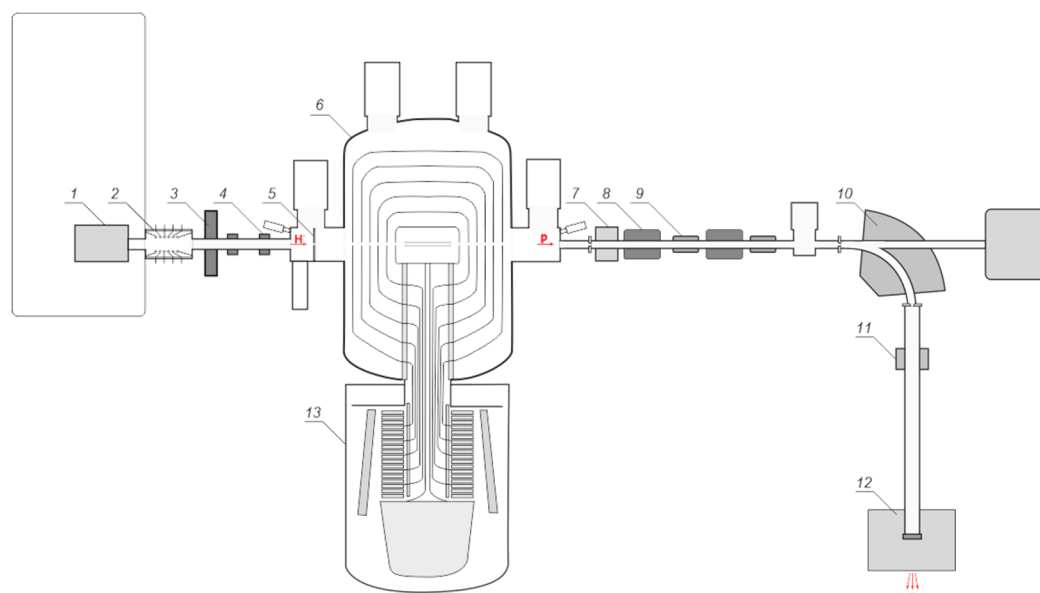


Figure 4. Scheme of the VITA-II β facility: 1 – negative ions injector, 2 – pre-accelerator, 3 – solenoid, 4 – correctors, 5 – accelerator input diaphragm, 6 – tandem accelerator, 7 – current meter, 8 – quadrupole lenses, 9 – correctors, 10 – bending magnet (proton beam is rotated in horizontal plane), 11 – beam absorber, 12 – lithium target and beam shaping assembly, 13 – high-voltage power supply. Arrows show propagation of negative hydrogen ions (H⁻), protons (p) and neutrons (n).

3. Results

3.1. New Boron Delivery Drugs

Currently, sodium borocaptate (BSH) and boronophenylalanine (BPA) are used for BNCT [12]. The development of new boron delivery drugs is relevant for improving therapy and expanding the range of tumor types. A significant number of new drugs have been tested in cell cultures and laboratory animals on the VITA facility. References to 10 articles with the results of testing new boron delivery drugs are given in [9]. One of the drugs was tested in the treatment of a domestic cat and it showed quite acceptable accumulation [13].

3.2. Pet Therapy

Thirty-three pets (cats and dogs) with spontaneous tumors were treated, primarily with BPA, and in six cases with gadolinium. In this case control groups were not formed, since neutron capture therapy was used in these animals with spontaneous tumors as an experimental palliative therapy, given the fact that by the time neutron capture therapy was conducted, all possible treatment options in each specific case had already been exhausted. Pets were not randomized. Irradiation occurred between 1:00 PM and 5:00 PM. The experimental unit – a single animal.

The first 9 cases with BPA are described in the article [14]. The data obtained indicate a partial tumor response when performing BNCT.

The next 7 incurable pets with spontaneous tumors were treated using gadolinium (Magnevist®, 0.6 mL/kg b.w.) as a neutron capture agent (gadolinium neutron capture therapy). The use of gadolinium for neutron capture therapy had no significant effects on the life expectancy and quality of life of animals with spontaneous tumors. Following this result, we stopped using gadolinium in therapy.

In the treatment of the last 10 pets, the method of prompt γ -ray spectroscopy was used to control the dose and to study the pharmacokinetics of the drug [13]. An hour prior to irradiation, an intravenous infusion of BPA solution with fructose in deionized water was started. The dosage of BPA was 700 mg per kilogram of animal weight, the solution volume was 20 ml per kilogram of animal weight. In one case, infusion of the drug was continued during irradiation. The primary outcomes of the animal therapy (tumor mass, irradiation parameters, boron concentration in blood) are presented and described in detail in [13]. The ongoing optimization of therapy and the experience gained yielded significant results: one month after therapy for the last pet (a cat with osteosarcoma of the mandible), the tumor volume decreased 26-fold, from 12.7 g to 0.48 g.

3.3. Dosimetry

3.3.1. Prompt γ -Ray Spectroscopy

The neutron capture reaction by boron itself provides a direct measurement opportunity since in 93.9% of cases one of the reaction products is the emission of a 0.478 MeV γ -quantum. The number of nuclear reactions that have occurred in the observed volume can be determined by measuring the intensity of radiation of photons with an energy of 478 keV. This method of measurement in relation to BNCT has been proposed and described in [15]; it is called the prompt γ -ray spectroscopy. Although this method is well-known, it is practically not implemented. The difficulty lies in the fact that the γ -ray spectrometer must be placed in the neutron flux and have good energy resolution. It must also be taken into account that photons of the same energy are also emitted from the lithium target due to inelastic scattering of protons on lithium nuclei. If a γ -spectrometer that is relatively resistant to neutron flux is used, its energy resolution will not allow the separation of the 478 keV line from the more intense 511 keV line. The HPGe γ -ray spectrometer separates these lines but is not resistant to neutrons. Efforts to introduce this method have been made for many years, but have been unsuccessful.

To implement this method of prompt γ -ray spectroscopy, we placed the γ -ray spectrometer as far as possible from the irradiation zone and protected it from neutrons as much as possible. We were

lucky that the bunker housing the neutron source was adjacent to another bunker (bunker 2, see Figure 1); the spectrometer was placed in it, behind a 1.5-meter concrete wall. A hole was drilled in the concrete wall to register radiation from the irradiation object. A collimator made of lead bricks was placed in front of the pet. A plexiglass plate, providing neutron scattering, was installed in front of the wall hole in bunker 1 for suppressing neutron penetration into bunker 2. A similar plexiglass plate was installed in bunker 2 in front of the spectrometer. The spectrometer detector was wrapped in cadmium foil to absorb thermal neutrons to ensure better safety of the spectrometer. The spectrometer detector was placed inside a lead collimator to reduce background signal and detector load. Measurements were performed using the SEG-1KP HPGe γ -spectrometer (Institute of Physics and Technology, Dubna) based on a semiconductor detector made of high-purity germanium.

The first application of prompt γ -ray spectroscopy to evaluate boron uptake and clearance during BNCT was performed on a cohort of ten pets [13]. A typical spectrum of the detected radiation is shown in Figure 5. It is clear that the 478 keV photon line can be reliably measured. It is also evident that this emission line is broadened due to the Doppler effect, since the photon emission occurs from a still-flying lithium-7 nucleus. Good registration of photons from the $^{10}\text{B}(n,\alpha)^7\text{Li}$ reaction is ensured by almost complete suppression of monochromatic 478 keV photons from the lithium target in the $^7\text{Li}(p,p'\gamma)^7\text{Li}$ reaction due to shielding of the lithium target with lead bricks and significant suppression of the neutron flux by placing plexiglass scatterers and cadmium foil. Other lines in the measured spectrum are noteworthy. The 511 keV line is due to annihilation processes; the 517 keV line is due to neutron capture by chlorine $^{35}\text{Cl}(n,\gamma)^{36}\text{Cl}$, and its intensity is proportional to the volume of tissue in the detection region; the 558 keV line is due to neutron capture by the cadmium foil ($^{113}\text{Cd}(n,\gamma)^{114}\text{Cd}$) that wraps the spectrometer detector, its intensity is proportional to the number of neutrons scattered from the detection region; the 1712 keV line is the single-escape peak for the 2.223 MeV line emitted during neutron capture by hydrogen $^1\text{H}(n,\gamma)^2\text{H}$, and its intensity is also proportional to the volume of tissue in the detection region.

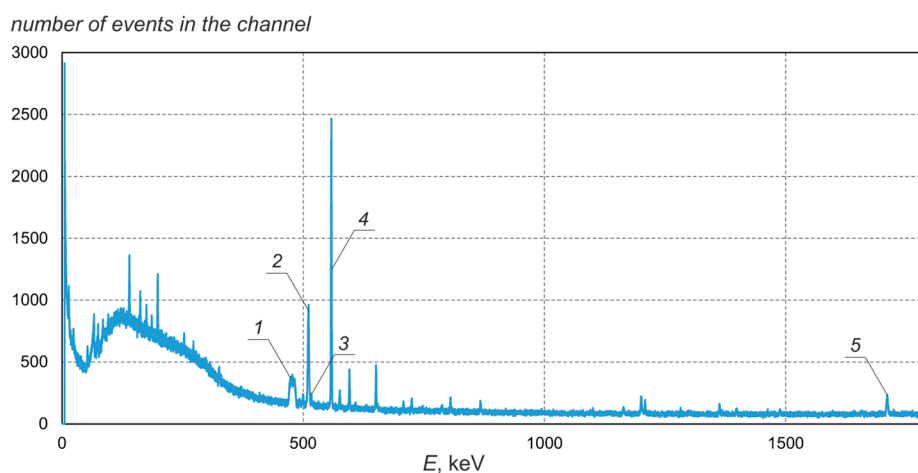


Figure 5. Characteristic energy spectrum measured by the γ -spectrometer: 1 – 478 keV, 2 – 511 keV, 3– 517 keV, 4 – 558 keV, 5 – 1712 keV.

Figure 6 presents the time dependence of the 478 keV line event count during one of the irradiations. Among all irradiated pets, the highest photon yield was recorded for this cat with adenocarcinoma in the nasal cavity, which was characterized by rapid tumor growth, indicating the greatest boron accumulation in the tumor. The graph also shows a rapid decline in boron accumulation; the signal reduction time by a factor of e is 3 hours. By moving the collimator and monitoring the 478 keV, 511 keV, 558 keV, 1.72 MeV and 2.223 MeV lines, data can be obtained indicating the selectivity of boron accumulation in the tumor.

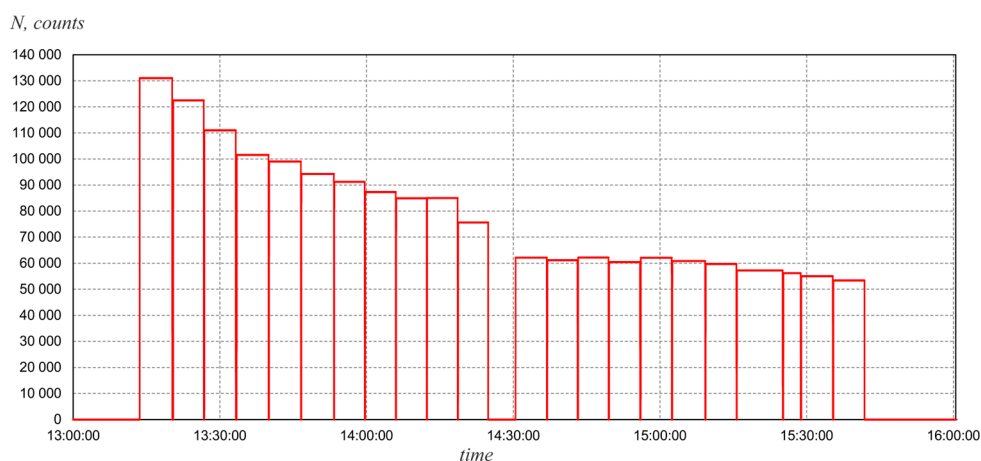


Figure 6. Dependence of the 478 keV line event count N (normalized to a proton fluence of 1 mA·h) on time during the one of the irradiations.

The studies revealed that the intensity of boron neutron capture nuclear reactions and the boron clearance time differ significantly in different pets: the former by a factor of 10, and the latter by a factor of 6. There was no correlation between the measured intensity of boron neutron capture events and the boron concentration in the tumor or blood. Attention should also be drawn to the differing dynamics of boron clearance from the tumor (ranging from 3 to 17 hours) and from the blood (ranging from 1 to 3 hours).

There are many potential factors that can cause interindividual variability in boron dynamics. To clarify this, we plan to conduct additional studies in 10 pets, limiting the variety of tumors and restricting the study design. We plan to treat pets with adenocarcinoma and use a mobile collimator to determine the time dynamics of boron accumulation in the tumor, in healthy tissue, and in the kidneys. We will also try to evaluate the therapeutic effect using ongoing assessment of animal condition.

The obtained data indicate that for therapy planning and outcome assessment, prompt γ -ray spectroscopy is strongly recommended for the treatment of patients using BNCT.

3.3.2. Compact Neutron Detector

A compact neutron detector has been developed and manufactured to measure the boron dose and γ -ray dose. The detector's sensors have identical design, each containing three independent optical detection channels. The first detection channel is based on a cast polystyrene scintillator with boron, the second is based on a similar scintillator without boron, and the third is an optical fiber without a scintillator. The scintillators are cylindrical, 1 mm in diameter and 1 mm long. The scintillators are mounted on the ends of the optical fiber using optical organosilicon rubber and protected by a light-tight plastic housing. The sides of the scintillator, as well as the end of the third optical fiber, are coated with a reflective coating. Light from the scintillators is transmitted via optical fibers to the readout electronics, and optical pulses are detected using micropixel avalanche photodiodes (SiPM). The number of registered events with an amplitude above a certain threshold at 10 ms intervals is transmitted to the computer for further processing. The difference between the counts of the two detectors, with and without boron, allows us to estimate the contribution of the neutron component recorded by the detector. The difference in the counts in the detector channel without boron and the number of events recorded in the channel without a scintillator produces a signal proportional to the γ -ray dose at the measurement point, since it eliminates the contribution of Cherenkov radiation generated in the optical fiber.

Using a compact neutron detector, we measured the spatial distribution of boron dose rate and γ -ray dose rate in air and in a water phantom for several variations of neutron beam shaping assembly

during its optimization. References to articles with the results of the development and use of the compact neutron detector are given in [9].

3.3.3. Cell Dosimeter

The use of a lithium target allows for a new method of measuring the sum of fast neutron dose and nitrogen dose. The idea is that at proton beam energies below the neutron generation threshold of 1.882 MeV, cell cultures can be irradiated with γ -radiation alone as a result of the ${}^7\text{Li}(p,p'\gamma){}^7\text{Li}$ reaction. At proton beam energies above the neutron generation threshold of 1.882 MeV, cell cultures placed in the same location are irradiated with mixed radiation: neutrons and γ -radiation. If the proton beam current is reduced to a certain value, then the same biological effect can be achieved, for example, the survival of cell cultures, by irradiating cell cultures with two different types of ionization for the same time. If irradiating cell cultures of the same line with two different types of radiation for the same duration results in equal cell survival, then the equivalent doses are equal. To implement this method, it is sufficient to measure the γ -ray dose D_γ , for which there are many measuring instruments. Hence, the sum of the fast neutron dose and the nitrogen dose (thermal neutron dose) D_n is calculated by the formula: $D_n = D_{\gamma\text{ standard}} - D_{\gamma\text{ mixed}}$, where $D_{\gamma\text{ standard}}$ – the γ -ray dose when the cells are exposed to γ -radiation; $D_{\gamma\text{ mixed}}$ – the γ -ray dose when the cells are exposed to mixed radiation.

3.3.4. Epithermal Neutron Flux Monitor

The epithermal neutron flux monitor is an activation detector using ${}^{71}\text{Ga}(n,\gamma){}^{72}\text{Ga}$ reaction [16]. This reaction is characterized by many resonances and by placing the activated material (gallium) inside the moderator, the same sensitivity to neutrons of different energies can be achieved. In the monitor, the activation material is positioned in the geometrical center of the polymethyl methacrylate (PMMA) or high-density polyethylene (HDPE) cylinder and covered with Cd foil for thermal neutron absorption. Numerical neutron transport simulation shows that the detector is sensitive to epithermal neutrons and it has a flat sensitivity curve in epithermal neutron range, while its sensitivities to thermal and fast neutrons are low. It was experimentally measured that the sensitivity of the flux monitor with HDPE moderator is 1.24 times higher than the sensitivity of the flux monitor with PMMA moderator. It is also proposed to equip the flux monitor with a titanium disk, which further reduces the detector's sensitivity to fast neutrons. References to articles with the results of the development and use of the epithermal neutron flux monitor are given in [9].

There is a problem with the available data on the ${}^{71}\text{Ga}(n,\gamma){}^{72}\text{Ga}$ reaction cross section. While in the resonance region the reaction cross sections are practically the same in ENDF-VII and JENDL-4.0 libraries, in the energy region below the resonances (below 50 eV), the cross section in ENDF-VII library is approximately 1.3 times larger than that in JENDL-4.0 library. For practical use of the flux monitor it is necessary to determine which of the used cross sections is reliable.

3.3.5. Labeling of the Boron Delivery Drug with Activated Nuclei

The idea is to label the boron delivery drug with a stable atomic nucleus characterized by a large neutron capture cross section. During irradiation, these atomic nuclei will become radioactive, and their spatial distribution can be measured with a γ -ray spectrometer after therapy. Nuclei such as ${}^{109}\text{Ag}$, ${}^{115}\text{In}$, and ${}^{197}\text{Au}$ are considered candidates. An approach to assessing the absorbed dose of BNCT using gold nanoparticles has demonstrated efficacy and safety in a cell culture experiment. Reference to article with this proposal is given in [9].

3.4. Fundamental Knowledge

When using an accelerator neutron source for treating patients, validation of the lithium target is required, including measurement of the neutron yield from the lithium target in the ${}^7\text{Li}(p,n){}^6\text{Be}$ reaction. The neutron yield from a lithium target was measured by its activation with the radioactive

isotope beryllium-7 using a γ -ray spectrometer based on a semiconductor detector made of high-purity germanium. The measured yield is shown to correspond to the calculated one [8] with an accuracy of 5%, which is important for planning the treatment.

The use of a lithium target entails additional emission of 478 keV photons as a result of inelastic scattering of a proton by lithium nuclei (${}^7\text{Li}(p,p'\gamma){}^7\text{Li}$ reaction). The accompanying photon absorbed dose is undesirable for BNCT. Knowing the photon yield of the ${}^7\text{Li}(p,p'\gamma){}^7\text{Li}$ reaction is certainly important for nuclear data evaluation and for estimating the absorbed dose when planning therapy. However, the data of the 478 keV photon yield and the data of the ${}^7\text{Li}(p,p'\gamma){}^7\text{Li}$ reaction cross section are few and differ significantly. We measured with high accuracy the ${}^7\text{Li}(p,p'\gamma){}^7\text{Li}$ reaction cross section and 478 keV photon yield from a thick lithium target at proton energies from 0.65 MeV to 2.225 MeV. The data obtained can help establish a benchmark for radiation protection and treatment planning. It is important to note that the results of measurements subsequently carried out by Greek and Iranian groups [17,18] coincide with those we measured with good accuracy.

3.5. Beam Shaping Assembly

The neutron beam shaping assembly (BSA) was optimized using numerical modeling of neutron and γ -radiation transport. The optimal range of neutron and proton energies, as well as the size and material of the moderator and reflector, were determined. The proton energy was 2.3 MeV, the moderator material was magnesium fluoride crystals, and the reflector material was graphite in the forward hemisphere and lead in the rear hemisphere. Using a compact neutron detector the calculations were verified, showing good agreement between the calculated and measured data. A view of the BSA for a Moscow clinic is shown in Figure 7. The neutron beam at 2.3 MeV 7 mA proton beam satisfies all IAEA requirements [2]: therapeutic epithermal flux is $5.6 \cdot 10^8 \text{ cm}^{-2} \text{ c}^{-1}$, thermal to epithermal ratio is 0.017, fast neutron dose per unit epithermal fluence is $6.5 \cdot 10^{-13} \text{ Gy cm}^{-2}$, gamma dose per unit epithermal fluence is $2.0 \cdot 10^{-13} \text{ Gy cm}^{-2}$.

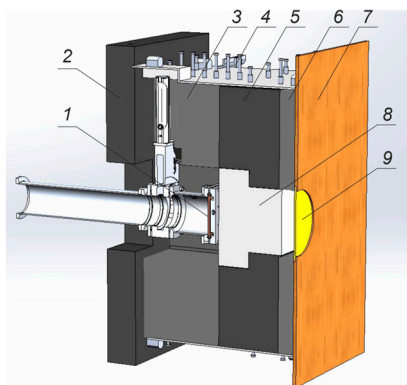


Figure 7. BSA: 1 – lithium target, 2 – curtains made of borated polyethylene, 3 and 6 – lead reflector, 4 – titanium frame, 5 – reflector made of reactor graphite, 7 – bismuth sheet, 8 – moderator made of magnesium fluoride crystals, 9 – filters.

In the article [19] the authors presented the depth distribution of the thermal neutron fluence rate, which is proportional to the boron dose rate, for accelerator neutron sources used for treatment or clinical trials. The data presented in this article allow us to compare the BSA we developed with similar ones.

Figure 8a shows the data on the depth distribution of the thermal neutron fluence rate in water, and Figure 8b – in PMMA. The legends in the figures mean the following: “VITA (Moscow)” is a 2.3 MeV 7 mA VITA-II β facility manufactured and delivered to the Moscow (Russia) for clinical trials; “Tsukuba” is an 8 MeV 4 mA radio-frequency accelerator with a beryllium target used in Tokai (Japan) for clinical trials; “Sumitomo” is a 30 MeV 1 mA cyclotron with beryllium target used in Osaka and Koriyama (Japan) for treatment; “Neutron Therapeutics” is a 2.6 MeV 30 mA single ended

accelerator used in Helsinki (Finland) for clinical trials; “VITA (Xiamen)” is a 2.35 MeV 10 mA VITA-II α facility manufactured and delivered to the hospital in Xiamen (China) used for clinical trials.

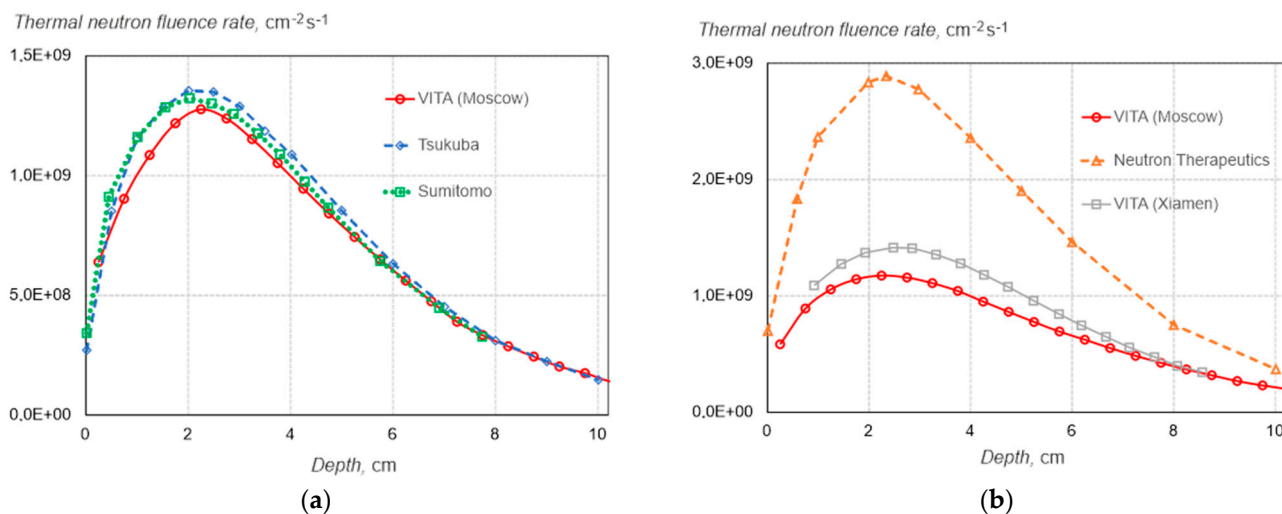


Figure 8. Depth distribution of thermal neutron fluence rate in water (a), in PMMA (b).

It is clear that the neutron beam we have formed allows us to obtain a similar deep distribution of the thermal neutron fluence rate, and consequently, the boron dose rate.

If we compare the facilities by efficiency (the ratio of the thermal neutron fluence rate to the proton beam power), we find that the VITA-II β facility is the most efficient: it is 2 times more efficient than the “Neutron Therapeutics” facility, 1.8 times more efficient than the “Tsukuba” facility, 1.75 times more efficient than the “Sumitomo” facility, and 1.2 times more efficient than the VITA-II α facility. The high efficiency is due to the use of a ${}^7\text{Li}(p,n){}^7\text{Be}$ reaction to generate neutrons, optimization of the lithium target and the use of magnesium fluoride crystals.

For scientific research with cell cultures and laboratory animals, the PMMA moderator is used at the VITA facility; since 2024, a HDPE moderator with a volumetric inclusion of bismuth has been used, the use of which has made it possible to halve the γ -ray dose while maintaining the boron dose.

3.6. Treatment Planning System

The VITA treatment planning system (TPS) is designed for therapy planning. VITA TPS is indispensable software for BNCT: it simulates a patient exposure using a three-dimensional model made of computed tomography (CT) data and provides calculation and analysis of dose distribution relationships that can be used to select optimal parameters for the therapy. VITA TPS software package consists of several modules: operator interface, geometry construction utility, particle transport simulation code NMC [20], ENDF-VII library of evaluated incident-neutron data, and gRPC server. VITA TPS has client-server architecture providing simultaneous work of several workstations.

VITA TPS interface is represented by a desktop application written in C# programming language. The interface allows processing CT data with subsequent creation of a voxel model of the patient which is further imported into the geometry construction utility of the particle transport simulation code NMC. The utility takes the voxel model and irradiation parameters set in a separate configuration file as an input. After building the geometry in a format that the particle transport modelling code accepts as an input, the program calculates the dose distributions in the model. The obtained data on the dose component distributions are transferred to the VITA TPS interface where they are combined with the original tomographic images of the patient and displayed as an isodose map.

Based on the overlap of the dose distributions and the specified contours of the regions of interest, the program output is a dose-volume histogram which is further interpreted by specialists

to decide on the possibility of BNCT. The patient data and irradiation plans are stored on the server to provide centralised data storage. The remote procedure call system (gRPC) is designed for communication between the client and server parts.

The output of TPS VITA is the exposure plan protocol which is a static representation of the exposure plan. The protocol includes longitudinal and transverse sections with the superimposed contours and the isodose map, and it contains statistics of the dose distribution in the contours. The standard approach to experimental validation of exposure plans is as follows: the patient's exposure conditions are transferred without changing any parameters to an available phantom using radiation detectors, then the phantom is irradiated, and the measured results are compared with the calculated ones. If the results of measurements and predictions for the phantom coincide, the plan is considered to be correctly calculated and the patient can be treated.

The calculation results were verified on the VITA facility in experiments with the measurement of boron dose and γ -ray dose in a water phantom for three different BSA: with a moderator made of magnesium fluoride crystals, with a moderator made of HDPE, and without a moderator. The study results demonstrated good agreement between the measured and modeled boron dose and γ -ray dose depth distributions for all cases considered. In all experiments, the maximum deviation between the calculated and experimental data for boron and gamma doses was comparable to the statistical error.

In section 3.3.1 we showed the possibility of using the prompt γ -ray spectroscopy method for BNCT which gives very important and reliable results. We highly recommend using this method of boron imaging in patient therapy. We have included the following additional features in the VITA TPS. The number of neutron capture reactions by boron-10 $^{10}\text{B}(n,\alpha\gamma)^7\text{Li}$ and the number of neutron capture reactions by hydrogen $^1\text{H}(n,\gamma)^2\text{D}$ within the field of view are calculated. The attenuation coefficient for the 478 keV photon flux in the direction of the γ -spectrometer and the attenuation coefficient for the 2.223 MeV photon flux in the direction of the γ -spectrometer are also calculated. Comparison of calculated and measured quantities of nuclear neutron absorption reactions by hydrogen, accounting for the attenuation of the 2.223 MeV photon flux in the direction of the γ -spectrometer placement, provides reliable verification of the neutron flux. Similarly, comparison of the calculated and measured numbers of nuclear neutron capture reactions by boron, accounting for the attenuation of the 478 keV photon flux in the direction of the γ -spectrometer placement, provides reliable determination of the boron concentration. This is important for treatment planning, determining the treatment duration, and evaluating the outcome.

We propose using a lithium target as a radionuclide source of 478 keV photons for the calibration of the γ -spectrometer. The radioactive isotope beryllium-7 is produced in the target upon irradiation with a proton beam *via* the nuclear reaction $^7\text{Li}(p,n)^7\text{Be}$. The resulting beryllium nuclei decay with a half-life of 53.22 days, emitting a 478 keV photon. The photon energy from this radionuclide source matches the energy of photons detected by the γ -spectrometer for boron dose measurement. Furthermore, the intensity of this photon source is comparable to the intensity of the emission measured by the γ -spectrometer for boron dose measurement.

3.7. VITA-III Facility

Let us recall that the second version of the VITA facility uses pre-acceleration of the beam of negative hydrogen ions injected into the accelerator.

At the VITA facility the proton beam has a transverse size 10 ± 1 mm, angular divergence from ± 0.5 mrad to ± 1.2 mrad, and normalized emittance 0.2 mm mrad. The transverse profile of the proton beam is well described by a Gaussian distribution. A typical phase portrait of a proton beam is shown in Figure 9a. An undoubted advantage of such a weakly divergent proton beam is the ability to deliver it to a lithium target without the use of focusing lenses. The only significant disadvantage of this injection mode is the heating of the uncooled diaphragm of the first accelerating electrode.

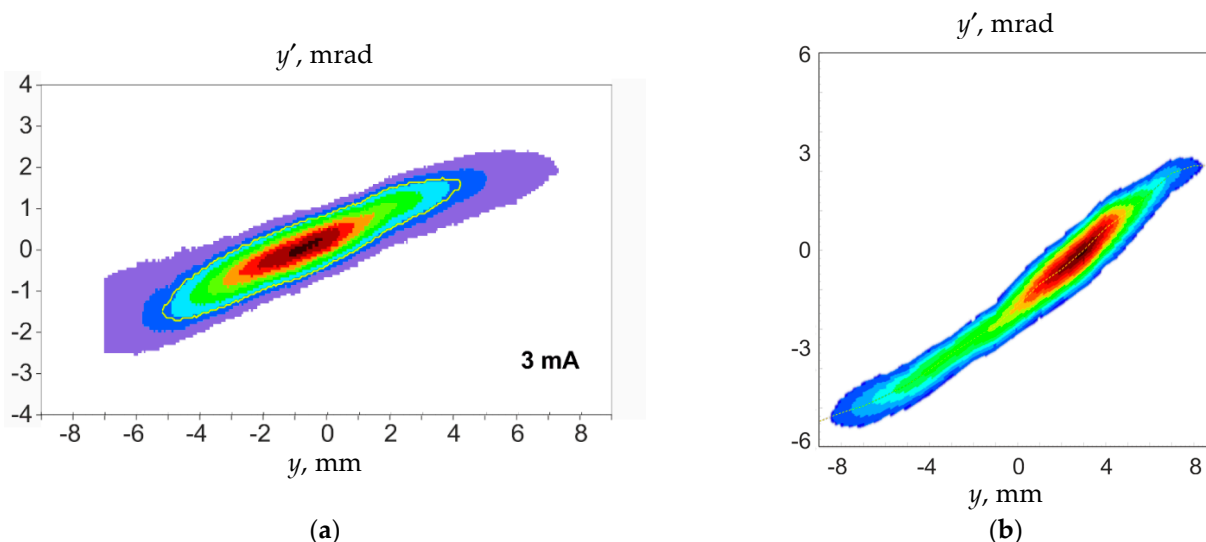


Figure 9. Phase portrait of 3 mA proton beam in VITA facility (a), in VITA-II facility (b).

At the VITA-II facility the proton beam has a transverse size 15-20 mm, angular divergence from ± 3 mrad to ± 4 mrad, and normalized emittance 0.2 mm mrad. The proton beam profile differs from the Gaussian distribution due to spherical aberrations of the pre-accelerator. A typical phase portrait of a proton beam is shown in Figure 9b.

The use of pre-acceleration has both positive and negative effects. The positive effect is that the proton energy is increased by 100 keV and there is no heating of the uncooled diaphragms of the accelerator due to the smaller size of the ion beam in the accelerator, especially at the beginning. The negative effect is that the quality of the resulting proton beam has deteriorated: it has become larger in size, non-uniform, and its divergence has become greater. Obtaining such a beam complicates the facility since focusing means are required for its transportation. The use of pre-acceleration itself also complicates the facility – a high-voltage platform and an isolating transformer are required.

To improve the accelerator, we proposed using de-accelerating of the injected ion beam instead of pre-accelerating it. This was achieved by isolating the input diaphragm of the accelerator and applying a negative potential to it. The implementation of de-acceleration made it possible to reduce the size of the ion beam in the region of the uncooled diaphragm and make the proton beam close to parallel. It's worth noting that significantly slowing down the injected ion beam dramatically improves the stability of the proton beam. The position of the proton beam is virtually independent of the injection angle of the negative hydrogen ion beam. This significantly increases the reliability of the facility.

The obtained result can be qualitatively explained as follows: the effect of the isolated diaphragm under potential is analogous to that of an Einzel lens, which focuses the ion beam. The de-acceleration and focusing of the ion beam into the diaphragm hole by the negative potential reduce its transverse momentum, thereby aiding the subsequent focusing by the input electrostatic lens of the accelerator.

During this study, it was also established that multiple Coulomb (Rutherford) scattering of ions on the atomic nuclei of the stripping gas (argon) in the stripper increases the normalized emittance of the proton beam by an amount comparable to the value of the normalized emittance of the beam of negative hydrogen ions injected into the accelerator, and this process already limits the size of the proton beam.

Thus, in the next version of the VITA facility we plan to abandon pre-acceleration and implement de-acceleration. To more quickly and reliably obtain the required voltage in the accelerator, we will use seven accelerating gaps instead of six. At the VITA facility, the gas stripper was replaced with a more compact one in 2024 (300 mm long instead of 400 mm, with a 12 mm hole diameter instead of 16 mm) and encountered no problems. Therefore, we will also use a more compact stripper in the VITA-III facility and will be able to maintain the same accelerator size with seven gaps.

3.8. Lithium Neutron Capture Therapy

Over the years since the advent of BNCT, the term has become virtually synonymous with NCT. This is partly due to the disappointing results of NCT with gadolinium. However, besides boron and gadolinium, several other elements possess high neutron capture cross-sections, with lithium occupying a special position among them.

The use of lithium instead of boron brings a new unique opportunity – local 100% energy release since all products of the ${}^6\text{Li}(n,\alpha){}^3\text{H}$ reaction have high linear energy transfer characteristics. Also, due to the longer range of the ${}^6\text{Li}(n,\alpha){}^3\text{H}$ reaction products, the requirements for homogeneous intracellular distribution of the neutron capture agent are less stringent. This reaction has remained largely unexplored, primarily due to the previously presumed high toxicity of lithium and the limited availability of lithium-6, which was considered a weapons-grade material.

Our 2023 article [21] marked the beginning of the era of lithium neutron capture therapy. First, we demonstrated in laboratory animals that natural lithium can accumulate in tumor cells to concentrations sufficient for therapy, and that its administration at these concentrations does not cause nephrotoxicity [21]. To study lithium nephrotoxicity male C57BL/6 mice of 10-12 weeks of age, with weights of 20-22 g were used. Tumor cells (B16 melanoma) were administered to animals (1×10^6 cell). After tumor growth was induced mice were randomly divided into eleven experimental groups ($n = 5/\text{group}$): a control group with an intact tumor and groups that treated by administering lithium carbonat at a single dose of 300 mg/kg or 400 mg/kg orally. The series of experiments for LiNCT was divided into 4 stages and was carried out using a total of 115 mice with implanted skin melanoma. Mice were sacrificed at 15 min, 30 min, 90 min, 180 min, and 7 days after the start of lithium administration. In the nephrotoxicity assessment experiment, descriptive statistics for lithium biodistribution in blood, tumor and organs, as well as the results of histological examination of the kidneys are presented in the corresponding publication [21].

Subsequently, for the first time worldwide, lithium neutron capture therapy was performed on tumor-bearing laboratory animals using lithium chloride enriched with a light isotope ${}^6\text{Li}$. To induce tumors, cultured B16 cells were injected subcutaneously into the right inguinal region of mice (2×10^6 cells). After tumor growth induction (10 days in the oral model and 7 days in the intraperitoneal drug administration model), mice were randomly divided in four groups: (1) a control group (intact tumor), (2) a group receiving only lithium, (3) a group receiving only radiation, and (4) a lithium neutron capture therapy group. Animals were randomly assigned to cages on different racks in the same room and maintained under standard laboratory conditions. Irradiation was administered between 1:00 PM and 5:00 PM. Tumor measurements were performed by a researcher blinded to group assignment. Animals were observed until death or euthanasia by cervical dislocation (without anesthesia) in compliance with the approved study protocol. In individual experiments where statistical analysis was conducted, it was performed using *R* language. The normality of the data was evaluated using the Shapiro-Wilk test, with a significance criterion of $p < 0.05$. Tumor volume dynamics was analyzed using a generalized linear mixed-effects model (GLMM). Kaplan–Meier curves were used to evaluate survival times. The log-rank test with Holm’s correction for multiple comparisons was used to estimate p-values based on the survival analysis results of the experimental animals. Two-tailed $p < 0.05$ deemed statistical significance. The results were striking: the treated group showed significantly increased survival and 2–4 times slower tumor growth compared to the three control groups.

Therefore, lithium should be regarded as a valid agent for NCT. Consequently, we call for a reconsideration of the current paradigm that positions boron as the sole agent for this therapy.

4. Discussion

The BNCT technique is beginning to enter clinical practice; several clinics are conducting the therapy, several clinics are conducting clinical trials, and several dozen more clinics are in the process of being established [2,3].

To obtain a therapeutic neutron beam in the epithermal energy range, various charged particle accelerators (cyclotrons, linear radiofrequency electrodynamic accelerators, electrostatic accelerators) with proton energies from 2.1 MeV to 30 MeV and various targets (lithium, beryllium) are used. Despite this diversity, *“accelerators producing very different initial neutron source spectra ultimately produce thermal neutron fluences in phantom which have a high degree of similarity”* [19, p. 5]. Further, in this article [19, p. 6] a very important statement was made: *“This promises much for the future of BNCT and will hopefully lead to the possibility of multi-centre trials of this important new cancer treatment technology”*.

Over time, this important new cancer treatment technology will require more accelerator neutron sources, and their efficiency will become more important. As follows from the results of the article [19], which presents data on the thermal neutron fluence rate of different neutron sources, and this can be seen in Figure 8, the use of a lithium target with a proton beam in the region of 2.3-2.5 MeV is more effective than the use of a beryllium target with higher proton energy. Electrostatic accelerators are characterized by greater efficiency than cyclotrons or linear radiofrequency electrodynamic accelerators. For these the reasons, simple, reliable, and efficient VITA-III accelerator neutron source appears to be a good candidate for equipping oncology clinics.

The aforementioned article [19] also touched on another important aspect: the need to produce a directed neutron beam. The IAEA's book [2] recommends a beam directivity greater than or equal to 0.7. The authors of the article showed *“that higher values (up to 0.87) provide some significant benefit for the introduction of dose verification approaches based on prompt-gamma imaging”*. However, they noted that *“it is feasible to generate a much more directional epithermal neutron beam, but with the cost of a significantly reduced intensity”*. Using the Birmingham facility as an example, they showed that increasing the neutron beam directionality from 0.62 to 0.67 leads to a decrease in fluence to 56%, and an increase the directionality to 0.87 leads to a decrease in fluence to 26%. We believe the cost of using a prompt γ -ray spectroscopy is prohibitively high, so we have proposed and implemented a solution that does not require neutron beam directionality. Details of the proposal are presented and discussed in sections 3.3.1 and 3.6.

We consider a prompt γ -ray spectroscopy to be important and reliable, and therefore recommend equipping oncology clinics with it. Its use will allow for adjustments in irradiation timing, if necessary, and more reliably evaluate treatment outcomes.

Other dosimetry methods are important for characterizing the neutron beam, but ultimately, for therapy, it's crucial to confirm the fast neutron dose, as it alone can vary significantly between different facilities. The other two undesirable doses (thermal neutron dose and γ -ray dose) [22], like the boron dose, are proportional to the thermal neutron flux density, and the only way to suppress them is to increase the ratio of boron concentration in the tumor to boron concentration in the healthy organs. We propose to use the *“cell dosimeter”* for measuring the fast neutron dose. Here it is important to remember that it is easy to suppress the fast neutron dose by thermalizing the neutron beam, but the depth of neutron penetration (depth of therapy) is reduced.

We believe it is important to study the effects of neutron irradiation on cell cultures and laboratory animals. A number of such studies have been conducted. It is clear that detailed studies of the mechanisms of cell death and changes in the tumor microenvironment are needed. Radiobiological studies are also needed to determine the relative biological effectiveness coefficients and the compound biological effectiveness under conditions typical for clinical use.

The IAEA recommendations [2] are formulated for a neutron beam of the epithermal energy range for the treatment of deep-seated tumors. As we know, an additional moderator is placed between the BSA and the patient when treating superficial tumors at the Kansai BNCT Medical Center (Osaka, Japan). We are currently developing a hydrogen-moderated BSA for the treatment of superficial tumors, which features a higher neutron beam intensity compared to traditional magnesium fluoride-moderated BSAs. In the future, accelerator neutron sources may need to be equipped with two BSAs: one for the treatment of deep-seated tumors and one for the treatment of superficial tumors.

In conclusion, we strongly recommend that efforts be made to develop lithium neutron capture therapy, which has several advantages over BNCT, or to develop a combination of the two that can provide a synergistic effect and preserve the imaging method.

5. Conclusions

Boron neutron capture therapy is considered a promising method for treating malignant tumors. Currently, several dozen accelerator neutron source projects are being implemented worldwide, with some of them being used for treatment or clinical trials. One of such sources is the VITA facility, consisting of a tandem electrostatic accelerator of an original design for producing a 2.3 MeV 10 mA proton beam, a lithium target for generating neutrons in the ${}^7\text{Li}(p,n){}^7\text{Be}$ reaction, and a beam shaping assembly for forming a neutron beam that meets IAEA recommendations.

The article describes the VITA facilities used for research or clinical trials, presents the results of the studies conducted and the dosimetry tools developed. The possibility of using the prompt γ -ray spectroscopy for boron imaging was experimentally demonstrated, its importance was noted, and a strong recommendation was given to equip oncology clinics with this diagnostic tool for planning therapy and assessing its results. The possibility of implementing the lithium neutron capture therapy, which has a number of advantages over BNCT, has been experimentally demonstrated, and its development is strongly recommended, possibly in combination with BNCT, which will allow the preservation of the direct imaging method. The VITA facility is distinguished by its highest efficiency, as shown by a comparison of thermal neutron fluence rate (boron dose) with other facilities. For this reason, the simple, reliable, and efficient VITA-III accelerator neutron source appears to be a good candidate for equipping oncology clinics.

6. Patents

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and S.S.; data curation, T.B. and A.Ko.; writing—original draft preparation, E.B., M.B., D.K., Y.K., E.S., and I.T.; writing—review and editing, S.T.; visualization, E.B., T.B., A.Ko., and T.S.; supervision, S.T.; project administration, S.T.; funding acquisition, S.T. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the Center for Genetic Resources of Laboratory Animals, Institute of Cytology and Genetics SB RAS, Novosibirsk, Russian Federation (protocol #91, approval date: October 05, 2021), by the Ethics Committee of the Research Institute of Clinical and Experimental Lymphology (protocol #194, approval date: November 29, 2024), and all manipulations were performed while respecting the principles of the humane treatment of animals (European Community Directive 86/609/EEC).

Informed Consent Statement: The ARRIVE checklist and pet's owner consent have been provided.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Abbreviations

The following abbreviations are used in this manuscript:

BPA	boronophenylalanine
BSA	beam shaping assembly
BSH	sodium borocaptate
BINP	Budker Institute of Nuclear Physics (Novosibirsk, Russia)
BNCT	boron neutron capture therapy
HDPE	high-density polyethylene
LiNCT	lithium neutron capture therapy
NCT	neutron capture therapy
PMMA	polymethyl methacrylate
TPS	treatment planning system
	1) Vacuum Insulated Tandem Accelerator
VITA	2) A trademark for the VITA accelerator neutron source, its components, software, and diagnostic equipment. Applies to physics research, medical research, clinical trials, and materials testing. The trademark was registered on April 22, 2026

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