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Current development status of accelerator-based neutron source for boron neutron capture therapy

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Abstract

Recently, progress in technology for accelerator-based neutron sources has increased attention regarding boron neutron capture therapy (BNCT). BNCT is a type of radiotherapy that combines neutrons and boron drugs and is expected to be used in the treatment of refractory and recurrent cancers. Owing to the need for high-intensity neutrons in treatment, compact accelerator-based neutron sources applicable to BNCT are being developed worldwide. These current projects utilize cyclotrons, linear accelerators, and electrostatic accelerators as accelerators for BNCT devices. Beryllium and lithium are the main target materials for neutron generation. The accelerators for BNCT device are required to accelerate charged particles with an average current ranging from a few milliamperes to a few tens of milliamperes in order to generate neutrons of sufficient intensity for the treatment. Moreover, the target systems require technologies and mechanisms that can withstand the large heat load produced by high-power beam irradiation and prevent blistering. This review outlines and explains the accelerator neutron sources for BNCT and the requirements for the components of each device, such as the accelerator, target material, and beam shaping assembly. In addition, various development projects for accelerator-based BNCT devices worldwide are introduced.

Keywords: Boron neutron capture therapy (BNCT); Accelerator-based neutron source; Target; Beam shaping assembly

1 Introduction

1.1 Overview of BNCT

Effective treatment methods have not yet been established for invasive cancers, including malignant brain tumors and recurrent cancers after conventional radiotherapy at the time of initial onset. In recent years, boron neutron capture therapy (BNCT) has attracted attention for the treatment of intractable and recurrent cancers [1]. BNCT is a type of radiation therapy that combines a neutron beam and a boron drug that selectively accumulates in cancer cells. Figure 1 shows the principle of BNCT. In the BNCT procedure, a boron drug is administered to the patient before irradiation. This combined drug contains enriched boron-10 attached to a compound that selectively accumulates in cancer

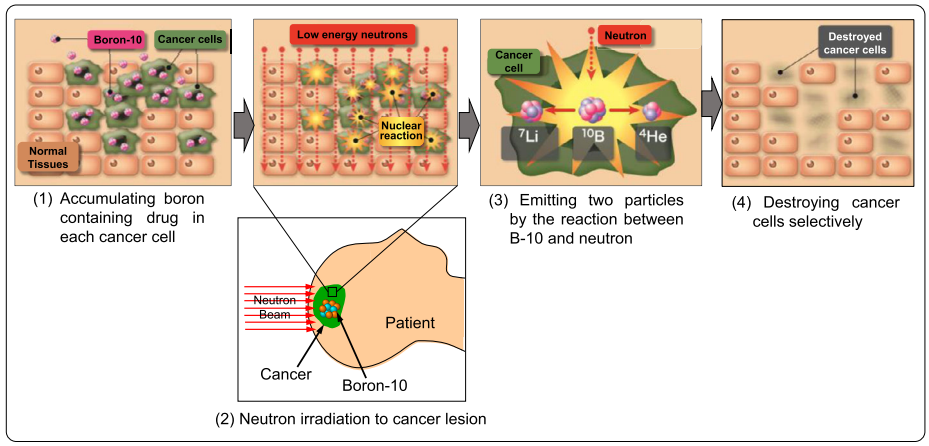

Figure 1 Principle of boron neutron capture therapy

cells. After this accumulation, the neutron beam irradiates the affected region. Boron-10 In the cancer cells reacts with neutrons to emit two particles (alpha particles and lithium nuclei). The range for both released particles is <10 μm, approximately that of human cells. Furthermore, the two released particles are heavy particles with a high cell-killing effect. Thus, the particles destroy only cancer cells and do not travel beyond them. Thus, this therapy can selectively destroy cancer cells and avoid damage to surrounding normal cells.

1.2 Reactor-based BNCT

BNCT requires a high-intensity neutron source as the therapeutic dose must be administered to a cancerous region within approximately 1 h. The International Atomic Energy Agency Current Status of Neutron Capture Therapy (IAEA TECDOC-1223) suggests an epithermal neutron flux of at least 5×10^8 (n/cm^2/s) as the intensity of the neutron source for BNCT [2]. Therefore, clinical trials on BNCT have been conducted using research reactors. In the early days of BNCT, clinical research began in the 1950s using research reactors at the National Brookhaven Institute and the Massachusetts Institute of Technology in the United States [3]. Since then, several clinical studies have been conducted using European and Japanese reactors. In addition, at the end of the 20th century, reactor-based BNCT spread to Argentina, Taiwan, and China. At that time, the treatment was conducted only on malignant melanoma, a type of skin cancer, and malignant brain tumors. Until the 1990s, irradiation was performed using thermal neutron beams (low-energy neutrons). In the treatment of malignant brain tumors, intraoperative irradiation, which involves surgical craniotomy, is used to deliver low-energy neutrons inside the brain [4]. Therefore, few clinical trials have been conducted in each reactor. However, since the 1990s, neutron sources that can generate epithermal neutrons (0.5 eV < E < 10 keV) have been installed in several reactors [5]. Using epithermal neutrons, a therapeutic dose can be delivered to a deeper region. The application of an epithermal neutron beam no longer requires craniotomy in BNCT for malignant brain tumors [6]. Furthermore, the application of BNCT has spread to head and neck, lung, and breast cancer, which have deeper lesions [7]. This was a significant breakthrough in BNCT, with further progression of BNCT research and development.

Clinical trials of 1,000 cases or more conducted on malignant brain tumors, head and neck cancer, malignant melanoma, etc. using research reactors worldwide have reported excellent treatment results. However, until recently, BNCT had not been established and spread worldwide as an effective cancer treatment method because it requires a nuclear reactor for treatment. Furthermore, it is difficult for reactors to obtain pharmaceutical approval for medical devices.

1.3 Accelerator-based BNCT

In recent years, attention has been focused on accelerator-based BNCT, which involves treatment using an accelerator-based neutron source [8]. Recent breakthroughs in accelerators and neutron generation technology have made it possible to generate neutrons of intensity comparable to that of a nuclear reactor using a compact accelerator installable in a hospital. Therefore, the successful development of a compact accelerator-based BNCT device enables patients to receive treatment in the hospital. Furthermore, as BNCT moves from clinical trials to advanced or insurance medical care, it is expected to be established and spread as a cancer therapy method. In this context, research and development of accelerator-based treatment devices for BNCT are currently underway worldwide. NeuCure, an accelerator-based BNCT device produced by Sumitomo Heavy Industry, Ltd. has been registered as a medical device for radiation therapy in Japan in 2020. And thus, BNCT with insurance medical care has been initiated using this device and many patients have already received treatment in two hospitals in Japan. As of 2023, clinical studies are still being conducted in Japan, China, and Korea using accelerator-based BNCT devices produced by several manufacturers.

The next section outlines accelerator-based neutron source devices applicable to BNCT and the requirements for the various components that form the device. The development status of accelerator-based BNCT devices is explained in the third section.

2 Accelerator-basEd neutron sourceS for BNCT

2.1 Overview of accelerator-based neutron sources for BNCT

Figure 2 shows a schematic of an accelerator-based BNCT device. Neutrons have no electric charge and cannot be accelerated directly. Thus, to generate neutrons, an accelerator is used to accelerate the charged particle to several or a few tens of mega-electronvolts. The particle is then irradiated to target materials and neutrons are generated secondarily from the target material. The energy of most neutrons emitted from the target material is generally higher (from a few hundred kilo-electronvolts to mega-electronvolts) than that of the neutrons applied for treatment. Hence, the neutron energy is reduced by passing through the device moderator. These adjusted neutrons are then released from the beam aperture behind the device before finally being administered to the patient. Several types of accelerators are currently being adopted in BNCT devices. The details of the device components are explained later.

Figure 2 shows also energy at each point for neutron and proton in the accelerator-based BNCT device. For BNCT treatment using "BPA" as the current standard boron compound, it is essential to complete the irradiation within 1 hour due to BPA's persistence in cancer cells and the patient comfort. Completing irradiation within 1 hour requires delivering a thermal neutron ($E < 0.5$ eV) flux of $\geq 1 \times 10^9$ (n/cm^2/s) around the cancerous region in the patient's body [2]. Here, in current BNCT, the epithermal neutron ($0.5 < E < 10$ keV) is used

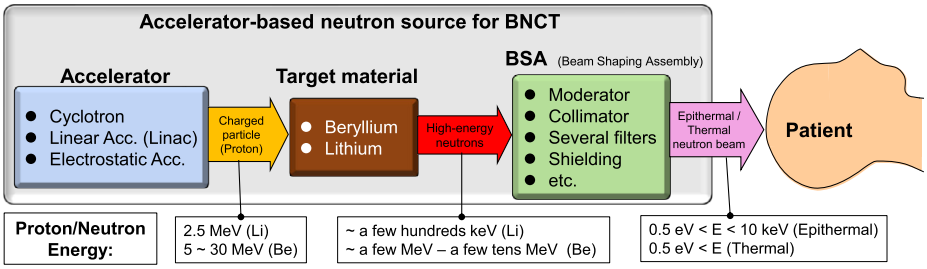

Figure 2 Schematic diagram of an accelerator-based neutron source for BNCT

for irradiation. The epithermal neutrons entering the body change to thermal neutrons by reacting with hydrogen in the body. By this reaction, thermal neutron flux builds up and then reaches as approximately twice the intensity of the epithermal neutron flux at a depth of around 2 cm within the body. Thus, $\geq 5\times10^{8}$ (n/cm^2/s) epithermal neutrons must be emitted from the beam aperture, which requires the release of approximately 1×10^{11} to 10^{12} (n/cm^2/s) high-energy neutrons by the reaction between the target material and primary charged particle.

2.2 Development challenges for accelerator-based BNCT devices

As mentioned above, the neutron source for BNCT requires generating a neutron intensity $\geq 1\times10^{11}$ to 10^{12} (n/cm^2/s) from a neutron target using a compact accelerator installed in a hospital. The neutron intensity is approximately 100 times that of typical compact accelerator-based neutron source devices for research use, such as the RANS of RIKEN, which is a representative device in Japan [2]. In other words, BNCT using a compact accelerator installed in a hospital requires a technology that generates 100-fold or higher neutrons at the same scale and size as conventional small accelerator neutron source devices. Hence, the main issues in the development of accelerator-based BNCT devices are as follows.

(1) Development of a compact accelerator that can accelerate and handle high-current particles ranging from several milliamperes (mA) to several tens of mA.

(2) Development of neutron generation target technology that can register both higher heal load and blistering damage due to the huge power particle beams of several tens of kilowatts (average current (mA) × energy (MeV)).

The following requirements also must be met as medical devices:

(3) Reduced reactivation of a device to suppress radiation exposure to patients and medical stalls as much as possible.

(4) Stable and continuous generation of neutron beams of consistent quality.

(5) Easy short-term maintenance

2.3 Primary particles and target materials

Regarding primary particles, protons are generally used as accelerator-based neutron sources for BNCT devices. Some research groups have also proposed the use of deuterons [9]. Several materials can be used as target materials according to the primary particle and its energy; for instance, beryllium, lithium, tantalum, and tungsten can be used as the target material when protons are used as the primary particle. Meanwhile, tantalum and

Table 1 Physical characteristics as target materials for lithium and beryllium

Materials and reactions	Proton energy (MeV)	Yield (neutron/proton)	Melting point (°C)	Heat conductivity (W/m/K)	Max. neutron energy	Moderator size
^{7}Li(p,n)^{7}Be	2.5	1.46×10^{-4}	180	84.7	100∼500 keV	Small
^{9}Be(p,n)^{9}B	4.0	1.60×10^{-4}	1278	201	2.1 MeV	↓
^{9}Be(p,n)^{9}B	30.0	3.00×10^{-2}	1278	201	28.1 MeV	Large

tungsten are used as the target material for high-energy protons. Finally, beryllium (Be-9) and carbon-13 have been proposed as candidates for the target material for deuterons are used as the primary particle [10]. Current accelerator-based BNCT devices generally use protons with relatively low energies (<30 MeV). Thus, beryllium or lithium is generally used in these devices. Each material has advantages and disadvantages. Some of the physical characteristics of both materials as target materials are listed in Table 1.

As mentioned in the previous section, generating the neutrons required for BNCT using an accelerator-based neutron source requires the irradiation of the target material with protons of several kilowatts to several tens of kilowatts. Thus, the target material will receive a high heat load of several tens of MW/cm^2. Therefore, it is necessary to develop a system that can withstand this heat load. In addition, when protons are used for primary particles, a large amount of hydrogen accumulates in the materials forming the target system due to the large number of protons present. This causes a phenomenon called "blistering," which can quickly destroy the target material. Thus, device developers also must consider a mechanism and technology to withstand blistering.

2.3.1 Lithium

When lithium is used as the target material, neutrons are normally generated via a resonance reaction with a proton of approximately 2.25 MeV. Thus, the acceleration energy of protons is approximately 2.5 MeV. Because the neutron generation efficiency (yield), as shown in Table 1, is smaller than that of beryllium, the average current of the protons incident on lithium is larger than that of beryllium. Specifically, an average current of 10–30 mA is required. However, the melting point of lithium is approximately 180°C which is lower than that of beryllium. Its thermal conductivity is also smaller than that of beryllium. As mentioned above, significant heat (tens of kW/m^2) is transferred to the lithium due to a proton beam irradiation of approximately 25–75 kW (2.5 × 10–30 mA). Therefore, more advanced cooling technologies are required for the target material system in lithium-based neutron sources. To solve this heat load issue, some groups have proposed using liquid lithium as a target material [11]. If liquid lithium is adopted, the target system should be constructed with due consideration when handling this material in hospitals. In addition, when lithium reacts with protons to generate neutrons, it changes to beryllium-7, with a half-life of approximately 53 days. Therefore, it is necessary to manage this radioisotope with a relatively long half-life. However, the advantage of lithium as a neutron source is that the energy of the incident protons is relatively low (approximately 2.5 MeV). Thus, the accelerator can be smaller than that of a beryllium-based neutron source. In addition, because the maximum energy of the neutrons emitted from lithium is several hundred kilo-electronvolts, the sizes of both moderators for producing epithermal neutrons and shielding walls can be reduced. This allows for a smaller building to house the device; thus, it may also contribute to reducing the initial cost of the facility.

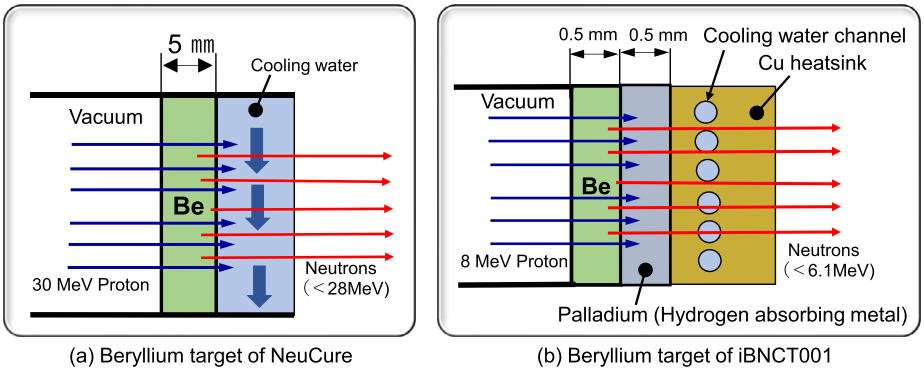

Figure 3 Schema of the beryllium target systems for NeuCure (SHI) (a) and iBNCT001 (Tsukuba-Group) (b) devices

2.3.2 Beryllium

When beryllium is used as the target material, the generation efficiency (yield) of the emitting neutrons is larger than that of lithium. The melting point is approximately 1287°C and its thermal conductivity is also higher than that of lithium. Thus, designing and producing a beryllium-based neutron target system may be easier than that for lithium. However, these factors change depending on the energy of the incident protons, as shown in Table 1. That is, the same incident charge on beryllium can generate more neutrons by injecting protons with higher energy. The higher the proton energy, the deeper the Bragg peak depth in beryllium; thus, it is possible to increase the thickness of beryllium. However, the maximum energy of the generated neutrons also increases in proportion to the energy of the incident protons because the Q value for this reaction is −1.9 MeV. In addition, several materials forming the device become radio-activated as they react with higher-energy neutrons emitted from beryllium. Furthermore, irradiating beryllium with a proton beam with >13.4 MeV changes it to beryllium-7 as a radioisotope. Thus, from the perspective of radio-activation and device miniaturization, it is better to decrease the energy of the incident protons. Thus, this is a trade-off. Therefore, when using beryllium as the target material, developers must consider these factors to determine the optimum proton energy.

Figure 3(a) shows the target system of the NeuCure device produced by Sumitomo Heavy Industry, Ltd. (SHI). The beryllium is 5 mm thick, which is relatively high due to the proton beam energy of 30 MeV. Thus, the beryllium plate also functions as a beam window for the beam transport system, while generating neutrons. Furthermore, because the cooling water can flow behind the beryllium plate while contacting the plate, it can directly cool the plate. Because protons stop in water but not beryllium, blistering of the beryllium plate can be avoided.

Figure 3(b) shows the beryllium target system of the iBNCT001 from Tsukuba-Group [12]. The proton beam energy is 8 MeV, lower than that of the NeuCure device. The Bragg peak depth of the 8 MeV proton in beryllium is approximately 0.55 mm. Thus, the thickness of the beryllium plate was set to 0.5 mm to avoid the accumulation of protons inside the beryllium plate. A second, 0.5 mm thick palladium plate is placed behind the beryllium plate. Because palladium is a hydrogen-absorbing metal, a large number of protons passing through the beryllium plate can be stored in the second layer; thus, breaking of the

target system in short term can be avoided. Furthermore, a third (copper) layer acting as a heat sink is placed behind the palladium plate. The copper block contains cooling water channels to cool the three materials. The three-layer-structured beryllium target system generates stable and continuous high-intensity neutrons under the operating conditions of an average proton current of 2.1 mA.

2.4 Accelerators

As previously mentioned, the accelerator for BNCT must accelerate primary particles (protons) with an average current from several milliamperes to a few tens of milliamperes. Lithium targets require approximately 2.5 MeV to perform this acceleration, while beryllium targets require that protons be accelerated from a few mega-electronvolts to a few tens of mega-electronvolts depending on the average current and target design. Currently, cyclotrons, electrostatic accelerators, and linear accelerators (Linac) are used as accelerators for BNCT.

2.4.1 Cyclotron

Cyclotrons increase particle speed to high energies using a relatively compact device. This type of accelerator has become widespread in other medical fields. However, it is difficult to achieve a large average current of tens of mA; a few mA may be their limit. SHI, one of the first BNCT manufacturers, uses a cyclotron in their BNCT device (NeuCure) [13]. The proton energy is proton is 30 MeV and the average current is 1 mA. The device is combined with a beryllium target.

2.4.2 Linac

Linacs can accelerate particles to low (several mega-electronvolts) and high (a few tens of mega-electronvolts) energies. They can also handle particles with large average currents of several tens of mA. Therefore, this accelerator can be used with both beryllium and lithium targets. However, the higher the energy of the particles, the larger the accelerator size. Therefore, the maximum proton energy of a linac applied to a BNCT device is approximately 10 MeV. The linac of a BNCT device generally adopts a radio frequency quadrupole (RFQ)-type linac as the first accelerator type. For the second and subsequent accelerators, a drift tube linac (DTL) is combined. A linac requires peripheral equipment, including a high-frequency power source, in addition to the main accelerator tube(s). Thus, the scale of the device is larger than that of the electrostatic accelerator, as described later.

The BNCT device (CICS-1) installed at the National Cancer Center Hospital in Japan uses a linac for proton acceleration [14] combined with a lithium target. Thus, the linac consists of only an RFQ owing to the proton energy of 2.5 MeV. The average current is $\geq$20 mA. However, in clinical use, the device is operated at 12 mA, owing to the priority of stability.

The BNCT device (iBNCT001), developed by the Tsukuba Group, uses a linac as a proton accelerator [15]. And beryllium has been adopted as a target material, leading to the proton energy being set at 8 MeV. Consequently, the linac consists of one RFQ and one DTL with the combined length of the two linac tubes being approximately 8 m. Figure 4 shows the linac consisting of an RFQ and a DTL of the iBNCT001 installed in the accelerator room of a BNCT facility. The linac has been designed to operate with an average current of $\geq$5 mA. As of 2023, the linac is currently operating with an average current of 2.1 mA.

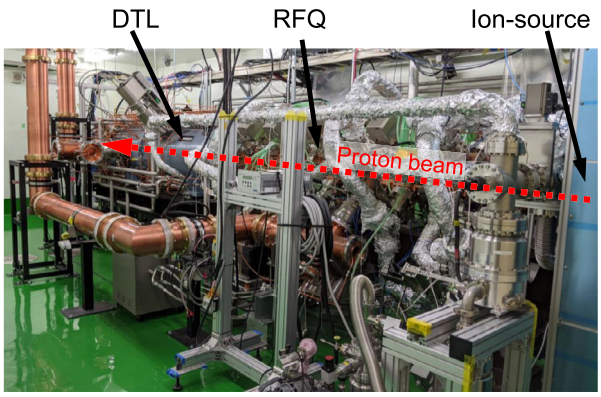

Figure 4 Linac tubes of the RFQ and the DTL of an iBNCT001 device installed in an accelerator room

2.4.3 Electrostatic accelerator

While electrostatic accelerators can accelerate particles of several tens of milliamperes, they are not suitable for accelerating particles with large currents to high energies. Therefore, this type of accelerator is usually used in combination with a lithium target because the accelerating energy of the protons is approximately 2.5 MeV. Electrostatic accelerators can be relatively compact compared to linac-based devices because they do not require peripheral equipment such as high-frequency power sources. Thus, the building can also be made smaller and the initial cost may be relatively lower. Except for the CICS-1, most BNCT devices combined with lithium targets have adopted electrostatic accelerators for proton acceleration.

The electrostatic accelerator-based BNCT device produced by Neutron Therapeutics Inc. accelerates protons to 2.6 MeV. The device has been installed at the Helsinki University Hospital in Finland [16]. While the device can drive an average current of 30 mA, this is reduced to 12 mA in clinical use.

2.5 Beam-shaping assembly (BSA)

Neutrons emitted from the target materials contain a large number of fast neutrons (E > 10 keV) with higher energy levels than those of epithermal (0.5 eV < E < 10 keV) or thermal (E < 0.5 eV) neutrons used for treatment. In particular, neutrons emitted from a beryllium target include high-energy (MeV) neutrons. Therefore, a BSA are typically installed behind the target material. The primary role of the BSA is to reduce and adjust the energy of neutrons using several materials. The neutrons passing through the BSA are released from the beam aperture attached to the end of the BSA to the patient. The size and location of each material in the BSA depend on the characteristics (energy spectrum and distribution) of the neutrons released from the target materials. Thus, the BSA design differs for each BNCT device manufacturer. The BSA is generally formed by "fast neutron filters", a "moderator", a "low-energy filter", a "gamma ray filter", "collimators", and "shielding. Most technologies and materials used in reactor-based BNCT can also be applied in the design and manufacture of BSA of accelerator-based BNCT device. A typical BSA of a BNCT device is shown in Fig. 5.

The maximum energy of epithermal neutrons for effective therapy is approximately 10 keV. Neutrons with energies higher than this can adversely affect normal tissues. Hence,

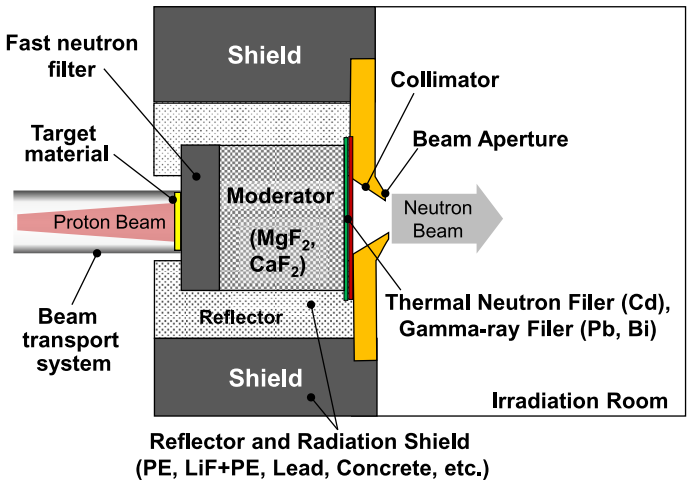

Figure 5 Schematic image of a typical beam shaping assembly for an accelerator-based BNCT device

first, the BSA should reduce the number of fast neutrons as much as possible. Thus, fast neutron filters are typically set behind the target material. In the case of a beryllium target, the maximum energy is in the range of several mega-electronvolts to a few tens of mega-electronvolts, although the maximum energy of neutrons from a lithium target is a few hundreds of kilo-electronvolts. Therefore, fast neutron filters for BSA using beryllium targets are generally larger than those of lithium-based devices. Moreover, fast neutron filters may be unnecessary in the case of lithium-based devices. Iron and lead are used as materials for fast-neutron filters, the sizes and thicknesses of which depend on the neutron energy and intensity.

The energy of neutrons that pass through a fast neutron filter is still too high to irradiate patients. Thus, a moderator to reduce and adjust the neutron energy is generally set behind the fast neutron filter in the BSA. When designing a moderator, a balance should be considered between the intensity and neutron spectrum of the neutron beam at the beam aperture. To eliminate the high-energy neutrons in the neutron beam as much as possible, the moderator should be larger in size and volume. However, in this case, the neutron intensity decreases at the beam aperture. Therefore, it is difficult to use a larger moderator, if the neutron intensity from a target material is not sufficient. Fluorides such as MgF_2 and CaF_2 are mainly used as moderator materials [17]. In addition, some materials applied to reactor-based BNCT devices, such as Fluental^{TM} (Al+AlF_3+Li), can also be used for the BSA of accelerator-based devices [18]. For the reasons explained above, the moderator of a device with a lithium target can be relatively small.

When using an epithermal neutron beam for treatment, low-energy neutrons (thermal neutrons) should also be cut further from neutrons passing through the moderator. In addition, the gamma rays mixed in the neutron beam should also be reduced as much as possible. Thus, thermal neutron and gamma-ray filters are usually installed behind the moderator in the BSA. Thermal neutron filters generally use cadmium several millimeters in thickness because of the large cross-section of capture in low-energy neutrons. In contrast, lead or bismuth are used for gamma-ray filters.

The neutrons, whose spectrum is adjusted by the moderator and several filters, are focused by the collimator to the beam aperture and finally released from the beam aperture

Table 2 Major accelerator-based BNCT devices under development worldwide

Country	Institute/Hospital	Accelerator type	Target material	Beam energy (MeV)	Beam current (mA)	Status
Japan	Southern Tohoku Hospital	Cyclotron	Be	30	1.0	Treatment
	Kansai BNCT Research Center	Cyclotron	Be	30	1.0	Treatment
	Kyoto University	Cyclotron	Be	30	1.0	Research
	National Cancer Center Hospital	Linac	Li	2.5	12	*1
	Edogawa Hospital	Linac	Li	2.5	12	*1
	University of Tsukuba	Linac	Be	8	2.1	*2
	Nagoya University	Electrostatic	Li	2.8	15	*3
	Shonan Kamakura Hospital	Electrostatic	Li	2.6	12	*3
Finland	Helsinki University Hospital	Electrostatic	Li	2.6	12	*2
China	Xiamen Humanity Hospital	Electrostatic	Li	2.5	10	*1
	IHEP	Linac	Li	3.5, 2.8	2.9, 20	*3
	China Institute of Atomic Energy	Cyclotron	Be	14	1	*5
	Lanzhou University	Electrostatic	Li	2.6	15	*5
Italy	CNAO	Electrostatic	Li	2.5	10	*5
	INFN	Linac	Be	5	30	*4
S. Korea	Gil Hospital	Linac	Be	10	8	*1
U.K.	Birmingham University	Electrostatic	Li	2.6	12	*4
Russia	Budker Institute	Electrostatic	Li	2.0-2.3	10	Research
Argentina	CNEA (deuteron)	Electrostatic	Be, C	1.45	30	*4
Spain	University of Granada	Electrostatic	Li	2.1	30	*5

*1: Clinical study, *2: Preparation of clinical study, *3: Commissioned, *4: Under development, *5: In planning

toward the patient. Collimators and beam apertures are composed of materials that can shield relatively low-energy neutrons. Specifically, compounds such as polyethylene contain large amounts of hydrogen or lithium fluoride. In BNCT, a circular aperture shape is typically used. Multiple beam apertures of different diameters are prepared in each facility, and a beam aperture of suitable diameter can be installed according to the size of the cancer lesion.

3 Projects related to accelerator-based BNCT devices worldwide

Accelerator-based BNCT devices are being developed by research institutes and manufacturers worldwide. In some cases, device prototypes are developed at national accelerator-related institutions. Several manufacturers and venture companies have also developed commercial-based BNCT devices, some of which have been installed in hospitals. These devices were designed and manufactured based on the assumption that they will be registered in pharmaceutical affairs. Table 2 shows a list of the major accelerator-based BNCT devices worldwide as of 2022.

Japan has conducted more projects for the development of BNCT devices compared to other countries. SHII is the first manufacturer of an accelerator-based BNCT device, the NeuCure cyclotron-based device, which was approved in Japan in 2020. The device has already been installed in two hospitals in Japan, and patients with recurrent head and neck cancer can receive BNCT using this device in insurance medical care [19]. A lithium target-based BNCT device, CICS-1 produced by CICS, a venture company, was installed at the National Cancer Center Hospital in Japan. Clinical trials for malignant skin tumors are currently being conducted to obtain regulatory approval for this device [20]. Furthermore, Tsukuba Group, with which the author has participated, developed a linac-based BNCT device. The details of its current status are presented in the next section. However, multiple devices have also been installed in hospitals outside Japan, with clinical trials on

Table 3 Major specifications of the iBNCT001 device and the characteristics of its neutron beam

Items	Values
Linac operating conditions	
Accelerator type	RFQ and DTL-type linac
Repetition cycle	75 Hz
Proton energy	8 MeV
Proton average current	2.1 mA
Target material	Beryllium
Neutron beam characteristics in free air	
Epithermal neutron flux	7.0×10^{8} (n/cm^2/s)
Gamma-ray dose rate in the epithermal beam	0.04 (Gy/h)
Ratio of thermal neutron per epithermal neutron	0.01
Fast neutron component per epithermal neutron	3.8×10^{-13} (Gycm^2/n)
Gamma-ray component per epithermal neutron	2.8×10^{-14} (Gycm^2/n)
Neutrons and gamma-rays in a water phantom	
Maximum thermal neutron flux	1.4×10^{9} (n/cm^2/s) (with 120 mm beam aperture)
Gamma-ray dose rate	5.0 (Gy/h)

actual patients planned for each. Neutron Therapeutics Inc., a venture company in the USA, has developed a BNCT device with an electrostatic accelerator. The first device has already been installed at the University of Helsinki Hospital in Finland, and BNCT treatment with this device is planned to be performed soon [16]. The second device was installed in Japan, for which clinical trials are planned. Another BNCT venture in the USA, TAE Life Science, is producing a commercial-based BNCT device based on the technology of a Russian accelerator neutron source. The first device was installed in a hospital in Xiamen, China, and BNCT treatment has begun to conduct in 2022. In recent years, many devices have been developed in Asia, particularly in South Korea and China. A BNCT facility in Korea has also begun to conduct clinical trials using linac-based BNCT device in the end of 2022.

4 Development status of iBNCT001 device

4.1 Outline of iBNCT001 in University of Tsukuba

The author is engaged in the development project of the "iBNCT", which was launched in 2011. The iBNCT project aimed to produce a demonstration linac-based BNCT device and to conduct clinical trials with actual patients using this device [15]. The iBNCT001 used a linac consisting of an RFQ and a DTL as the proton accelerator. The linac is shown in Fig. 5. Beryllium was selected as the target material, as described in Sect. 2.3. The RFQ accelerates the proton with an average current of 2.1 mA at 3 MeV, whereas the next DTL further increases the proton energy to 8 MeV. Neutrons are generated by irradiating 8 MeV protons onto a thin beryllium target. The device has successfully generated neutrons of sufficient intensity for BNCT. When the linac drives with an average current of 2.1 mA, the flux of epithermal neutrons is approximately 7.0×10^{8} (n/cm^2/s) at the beam aperture. Table 3 lists the major specifications of the iBNCT001. Figure 6 shows the irradiation room for the iBNCT001.

4.2 Neutron beam performance of iBNCT001

The iBNCT group is planning clinical studies in real patients using the iBNCT001. In order to conduct clinical trials, it is necessary to understand the characteristics of the neutron beam produced by the device from both a physical and biological point of view.

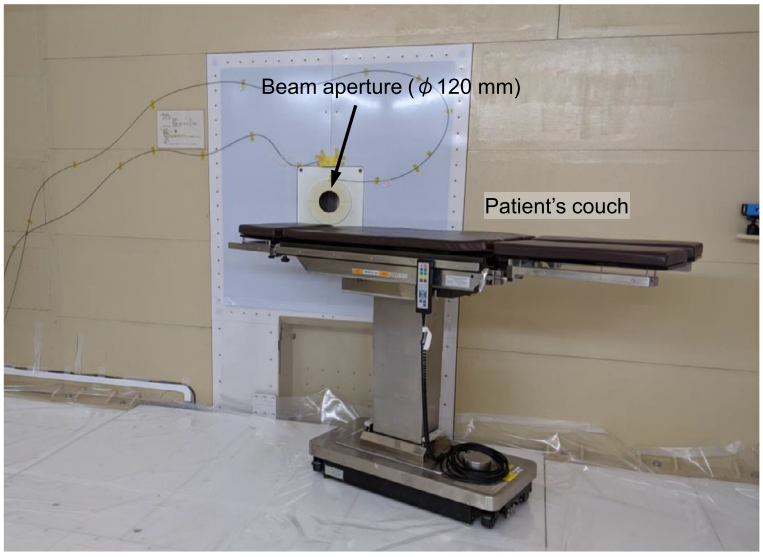

Figure 6 iBNCT001 irradiation room

Based on this, various measurements of the physical characteristics of the neutron beam have been performed [21, 22]. iBNCT001 has two beam aperture diameters of 120 and 150 mm. It is expected that the 120 mm diameter beam collimator will be used for most of the irradiation. If the tumor size is large, the 150 mm diameter beam collimator is used for irradiation. Figure 7 shows a picture of the experiments using the 120 mm diameter beam collimator and a rectangular water phantom was set at the irradiation position with the beam collimator. This water phantom simulates a human head, and detectors for measuring neutrons and gamma-rays can be placed inside. To measure two-dimensional distribution of thermal neutron flux in the phantom experimentally, many gold wires are installed in the phantom and the phantom was irradiated. The average current of proton beam in the experiments were set to 2.1 mA. After irradiation, the activations of each gold wire were measured using a germanium detector and the thermal neutron flux distributions inside the phantom were determined using the activation foil method. The measurements were performed on both 120 mm and 150 mm diameter beam collimators. Figure 8 shows thermal neutron flux distributions on the beam axis in the phantom for both beam collimators. The maximum flux for the 120 mm diameter beam collimator was measured to be approximately 1.36×10^9 $cm^{-2}s^{-1}$ at a depth of 20 mm from the phantom's surface. And for the maximum flux for the 150 mm diameter beam collimator was approximately 1.40×10^9 $cm^{-2}s^{-1}$ at the same depth. It was slightly higher than that of the 120 mm diameter beam collimator. Figure 9 shows the lateral distributions of the thermal neutron flux at a depth of 20 mm in the phantom for both diameters. Comparing the lateral distributions, there was no change in the difference between the two fluxes in the region from the central axis of the beam to 50 mm. However, as shown in Fig. 9, the flux difference increased from 50 mm outward, and the thermal neutron flux for the 150 mm diameter was greater than that for the 120 mm diameter.

The experimental results demonstrated that the device can generate sufficient neutron for BNCT therapy. First, the iBNCT group plans to conduct a clinical trial for malignant brain tumor. Based on the experimental results, it is expected that the irradiation against

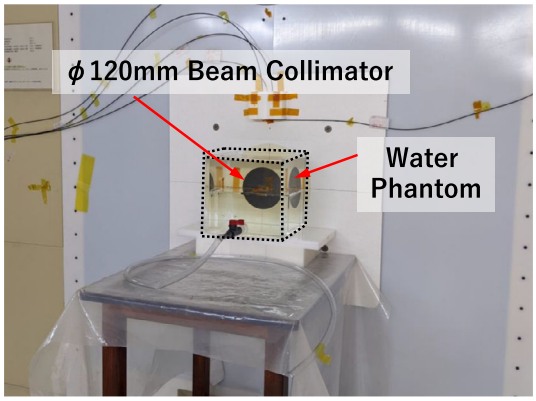

Figure 7 Water phantom experiment with 120 mm diameter beam collimator

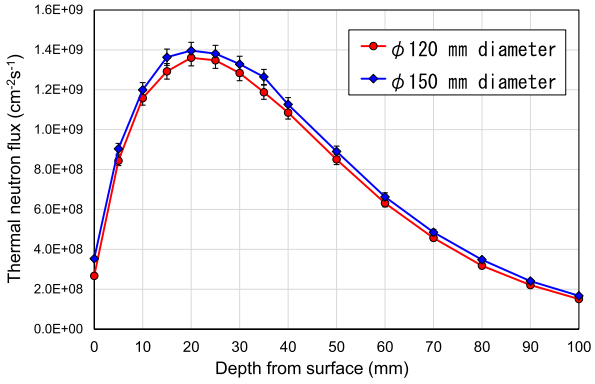

Figure 8 Thermal neutron flux distributions on the beam axis in the phantom for the 120 mm and the 150 mm diameter beam collimators

the malignant brain tumor can be completed in about 30 minutes. In addition to various physical measurements, non-clinical studies using mouse irradiation, which are necessary for conducting clinical studies, were also conducted in 2022. Based on the results of these experiments, a clinical study with actual patients will be conducted soon.

5 Conclusions

BNCT has shown excellent results in clinical research using research reactors. However, this technology could not be established as a cancer treatment method owing to its requirement for a nuclear reactor. Recent advances in technologies related to accelerator and neutron sources to develop compact accelerator-based neutron sources have allowed BNCT to be performed in hospitals. Many accelerator-based BNCT devices are currently being developed worldwide. The accelerator types adopted for BNCT devices include cyclotron, linac, and electrostatic technologies. A proton is usually used as a primary particle accelerated by accelerators, and beryllium or lithium are combined as the target material. To generate neutrons of sufficient intensity for BNCT, the accelerator should aim for a maximum average current of a few tens of mA. The target material must possess a mechanism that can withstand high-power proton irradiation and blistering.

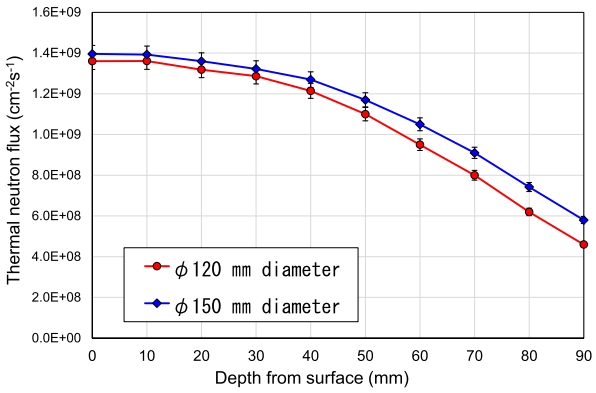

Figure 9 Lateral distributions of the thermal neutron flux at a depth of 20 mm in the phantom for both diameters

The NeuCure, a cyclotron-based BNCT device produced by SHI, was approved in Japan in 2020. The device is installed in two hospitals in Japan and has been used to provide treatment for recurrent head-and-neck cancer in insurance medical care since 2020. A clinical trial for malignant skin cancer using a BNCT device combined with a lithium target is underway at the National Cancer Center Hospital in Japan. The iBNCT group headed by the University of Tsukuba has also developed a linac-based BNCT device and the non-clinical studies required for clinical trials are currently being performed. Several BNCT devices are being developed in countries other than Japan, and treatments using these devices are planned. Therefore, BNCT is expected to become established and implemented as a standard cancer treatment.

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Availability of data and materials
The data that support the findings in this study are available from the corresponding author upon reasonable request.

Declarations

Competing interests
The authors declare that they no competing interests.

Author contributions
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