CURRENT DEVELOPMENT STATUS OF THE LINAC-BASED BNCT DEVICE OF THE IBNCT TSUKUBA PROJECT

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Abstract

In recent years, boron neutron capture therapy (BNCT) has attracted attention as a treatment for various cancers. As BNCT requires high-intensity neutrons for treatment, clinical studies worldwide have been conducted using research reactors. Recent progress in accelerator technologies has made it possible to perform BNCT using accelerator-based neutron sources instead of reactors. Hence, many institutes and manufacturers worldwide are developing compact accelerator-based neutron source devices for BNCT. In this context, the Ibaraki-Boron Neutron Capture Therapy (iBNCT) project is developing the "iBNCT001," a demonstration linear accelerator-based neutron source for BNCT. The iBNCT001 generates a neutron beam via a reaction between 8 MeV protons and a beryllium target. Currently, the linear accelerator (linac) of the iBNCT001 can operate with an average proton current of 2.1 mA. Experiments using a water phantom were performed to confirm the characteristics of the neutron beam. The measurement results proved that a maximum thermal neutron flux in the phantom of approximately 1.40×10^9 (n/cm^2/s) for a normal beam aperture 150 mm in diameter. The neutron intensity was sufficient to complete irradiation within 30 min for BNCT. Extended collimators protruding 100 mm from the wall were developed in addition to normal beam apertures. The extended collimators avoided interference between the patient's body and the wall during irradiation of head and neck cancers. The measurement results for the extended collimator proved that irradiation with the extended collimator can be completed within 1 h when for a neutron beam with an average proton current of 2.0 mA.

1. INTRODUCTION

In recent years, boron neutron capture therapy (BNCT) has attracted attention as a radiation therapy for intractable and recurrent cancer [1]. BNCT is currently categorized as radiation therapy because a neutron beam is irradiated from a beam irradiation device to the affected region of a patient. However, unlike conventional external radiation therapy, BNCT is considered a next-generation radiation therapy because it involves a reaction with a drug that accumulates in cancer cells. In BNCT, a drug that can selectively accumulate in cancer cells is administered to the patient before neutron irradiation. This drug contains concentrated (>99.9%) boron-10. Irradiation of the tumor region where the boron-containing drug is accumulated with a neutron beam causes the release of alpha-particles and lithium-7 in each tumor cell due to a reaction between low-energy neutrons and boron-10. The range for both released particles in the cells is <10 μm, which is approximately the same size as human cells. Furthermore, the two particles are high linear energy transfer (LET) particles. Thus, the particles selectively destroy tumor cells while avoiding critical damage to healthy tissues around the tumor, even in tumor cells infiltrating healthy tissues. Fig.1 shows a schematic of the BNCT principle.

However, this therapy requires a high-intensity neutron source. Clinical studies since the 1990s using epithermal neutron beams required an epithermal neutron flux of 5×10^8 (n/cm^2/s) or more at the beam aperture. The requirements for the neutron beam in BNCT were introduced in the International Atomic Energy Agency Current Status of Neutron Capture Therapy (IAEA TECDOC-1223) [2]. Therefore, BNCT has been performed worldwide using research reactors. Clinical studies of BNCT for the treatment of malignant brain tumors, head-and-neck cancer, malignant melanoma, etc. have been reported in 1,000 cases or more worldwide, with excellent results. However, until recently, BNCT has not been established and spread widely as an effective cancer treatment method due to the requirement for a nuclear reactor. It is difficult to build new reactors; moreover, in Japan, it is impossible to build a research reactor for installation in a hospital. In recent years, BNCT using an accelerator-based neutron source has attracted attention to address this limitation. Progress in technologies for both accelerator and neutron generation has made it possible to generate the neutrons required for BNCT treatment with a small accelerator. The availability of a small accelerator-based BNCT device in hospitals will allow patients to receive treatment. Furthermore, it is expected that BNCT can advance from clinical studies to insurance and advanced medical care. Therefore, many institutes and manufacturers worldwide are developing compact accelerator-based neutron source devices for BNCT. Among the first manufacturers is Sumitomo Heavy Industry Ltd., which produces "NueCure", a cyclotron-based BNCT treatment device [3]. The device was approved in Japan in 2020 and has been installed in two hospitals, with treatment using this device for head-and-neck cancer provided as insurance medical care in Japan since June 2020.

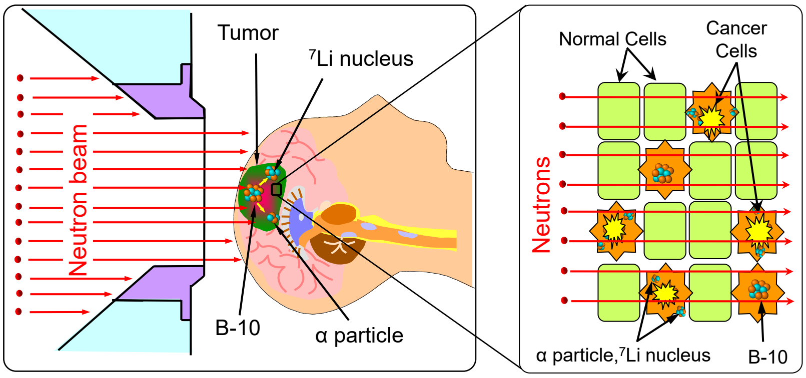


FIG.1. Principle of boron neutron capture therapy.

In this context, the "iBNCT," a project team aimed at developing an accelerator based BNCT device, was launched in 2011 [4]. The iBNCT project team, an industry-academia-government collaboration, includes the University of Tsukuba, the high-energy accelerator research organization, Japan Atomic Energy Agency, Ibaraki Prefecture, and several manufacturers related to the accelerator. This project is working to develop a a demonstration of an accelerator based BNCT device, iBNCT001, and has already successfully generated a neutron beam with sufficient intensity for treatment. We are currently preparing to conduct clinical studies using the iBNCT001 for future regulatory approval applications for this device. As part of this activity, we are performing experiments to measure the neutron beam characteristics of the device. In this project, new beam collimators that are effective for treatment were also developed and the characteristics of the collimators were measured.

The outlines of the device and the characteristics of the neutron beam obtained from the measurements are introduced.

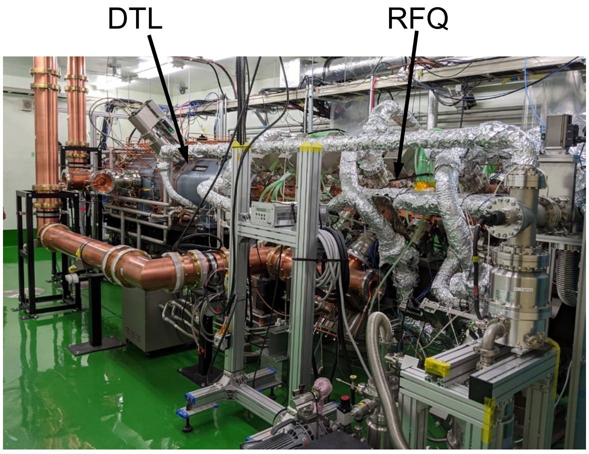
2. MATERIALS AND METHODS

2.1. Accelerator-based neutron source of the iBNCT001

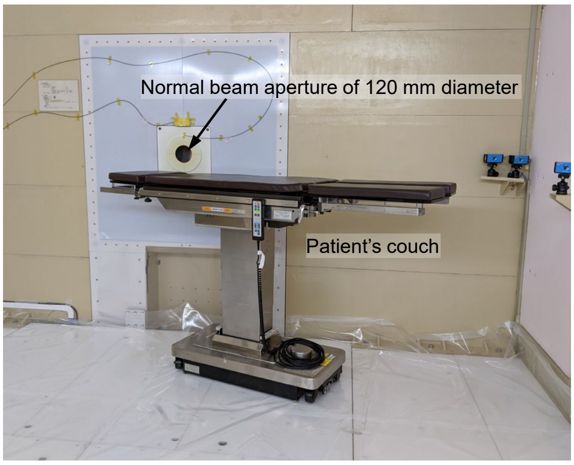
In the design stage of iBNCT001, the iBNCT team's accelerator-based BNCT device, we decided to adopt beryllium as the target material [5]. We next discussed the energy of the proton beam incident on the beryllium. To easily operate and maintain the device in a hospital, we believed that the radio-activation of the device by neutrons during treatment should be reduced as much as possible. However, high neutron intensity is also required. If the proton energy is too low, it is not possible to obtain the neutron intensity required for treatment. Based on various analyses, the proton beam energy was set to 8 MeV. The neutron energy emitted from the beryllium target by the reaction with 8 MeV protons is $\leq$6.1 MeV, which is relatively low. Therefore, the potential radio-activation of most of the materials forming the device will be suppressed. Treatment completion in <1 hour required the generation of epithermal neutrons with a flux of $\geq 5 \times 10^8$ (n/cm^2/s) at the beam aperture. To obtain this neutron intensity, protons of a few milliamperes have to irradiate to the beryllium. Hence, at the design stage, we set an average proton current of $\geq$5 mA in the accelerator. Finally, we chose a linear accelerator (linac) to produce the required proton beam. The linac of the iBNCT001 consists of a radio-frequency quadrupole (RFQ) and a drift tube linac (DTL). The first RFQ accelerates the proton from the ion source to 3 MeV, while the second DTL increases further the proton speed to 8 MeV. Fig. 1(a) shows the RFQ and DTL of the iBNCT001 installed in the accelerator room, while Fig. 1(b) shows the irradiation room of iBNCT001. The patient couch was set near a normal beam aperture of 120 mm. Table 1 lists the main specifications of the proposed device for the year 2022.

The energy of neutrons emitted from beryllium targets is higher than that of epithermal neutrons applied for treatment. Therefore, a beam-shaping assembly (BSA) that can adjust the energy of neutrons is placed between the beryllium target and the patient. The BSA of the iBNCT001 consists of a moderator, collimator, and shielding. The moderator cuts high-energy neutrons that are unnecessary for treatment and reduces their energy to the epithermal region. The collimator focuses the neutrons used for treatment on the beam aperture. Finally, the neutrons are released from the beam aperture toward the patient.

The beam aperture, which is attached to the edge of the collimator, can be changed depending on the tumor location and size. Several types of beam apertures have been developed, all of which are circular. The shapes of the beam apertures include "normal beam aperture," and "extended collimator." The position of the neutron release surface of the normal beam aperture is the same as that of the surrounding wall. Normal beam apertures with diameters of 120 and 150 mm have been prepared. However, in extended collimators, the neutron-release surface of the beam aperture protrudes 100 mm from the surrounding wall to create a space between the patient's body and the wall. The extended collimator is useful for irradiation, especially in patients with head and neck cancer, because it can suppress interference between the patient's shoulder and the wall. Extended collimators with diameters of 10, 120, and 150 mm have been produced.



(a) Linac of iBNCT001 installed in an accelerator room



(b) Irradiation room of the iBNCT001

FIG.2. Linac of the iBNCT001 installed in the accelerator (a) and irradiation (b) rooms.

TABLE 1. Main specifications of the iBNCT001

Items	Values
Accelerator type	RFQ and DLT type linac
Proton energy	8 MeV
Proton pulse width	1 ms
RF frequency	324 MHz
Average proton current	>5.0 mA
Target material	Beryllium
Diameter of the beam aperture	Normal beam aperture: 120 mm, 150 mm
	Extended collimator: 100 mm, 120 mm, 150 mm

2.2. Neutron beam performance of the iBNCT001

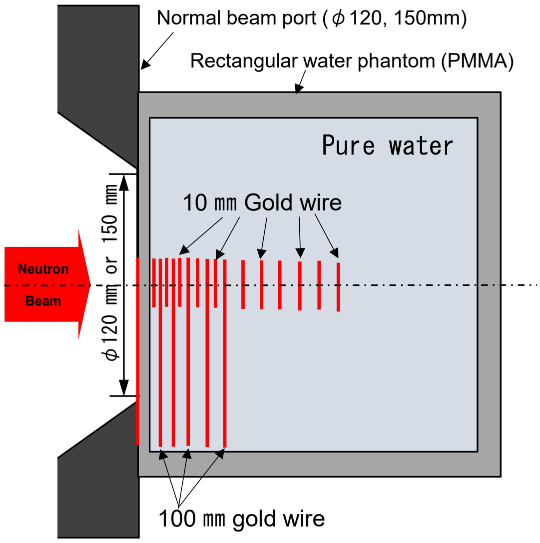
The production of the accelerator and BSA and the assembly of the iBNCT001 were completed in 2016. The neutron beam was successfully generated in the same year. However, at that time, the average current was as small as approximately 0.1 mA, which was not sufficient for treatment. Subsequently, the accelerator was improved and upgraded to incrementally increase the average proton current, with an average linac current of 1.4 mA by 2018 [6]. Furthermore, in 2019, the average current was 2.1 mA, with a stable and continuous neutron beam. In future BNCT treatment, we plan to perform irradiation by generating a neutron beam under operating conditions with an average current of 2.1 mA. We conducted various physical characterization measurements to confirm whether the neutron beam generated under this operating condition was applicable to treatment. First, the characteristics of the neutron beam emitted from the beam aperture were measured under free-in-air conditions. The neutron spectrum of the beam was measured using a Bonner sphere spectrometer [7]. The measurement results demonstrated that the device could generate epithermal neutrons as designed. The flux of the epithermal neutron was approximately 7.0×10^8 (n/cm^2/s) under the operating condition of an average current of 2.1 mA. This intensity was higher than that recommended by IAEA-TEC DOC-1223 and is sufficient for BNCT treatment. Table 2 shows several neutron beam characteristics based on the measurement results and Monte Carlo analysis.

TABLE 2. Beam characteristics of the iBNCT001 in free-in-air conditions

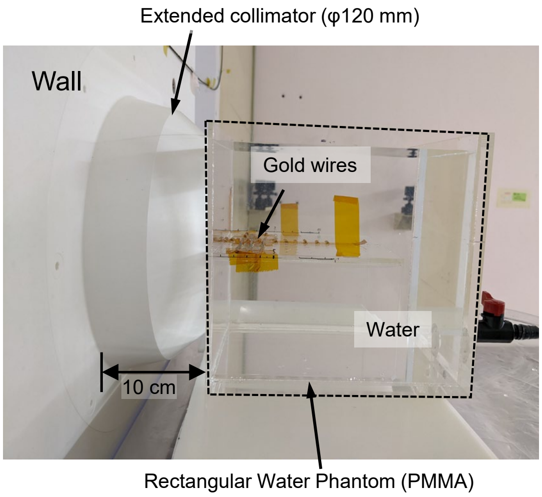
Items	Values
Linac operating conditions:	
Repetition cycle	75 Hz
Proton average current	2.1 mA
Beam Aperture	Normal beam aperture, 120 mm diameter
Neutron characteristics:	
Epithermal neutron flux	7.0×10^{8} (n/cm^2/s)
Gamma-ray dose rate in the epithermal beam	0.04 (Gy/h)
Ratio of thermal neutron per 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)

2.3. Water phantom experiments

To confirm the effects and influence of the iBNCT001 neutron beam when used to irradiate a living body, the physical characteristic measurements were first made during irradiation of a water phantom before conducting biological experiments in cells and mice. Fig. 3(a) shows a schematic of the experiments using the normal beam aperture, with a rectangular water phantom set to the irradiation position behind the beam port. Fig.3(b) shows a photograph of the phantom experiment to measure the distribution of the thermal neutron flux in the phantom with an extended collimator.



(a) Schema of the phantom experiment



(b) Phantom experiment with the extended collimator

FIG.3. Schema of the water phantom experiment (a) and a photograph of a phantom experiment with an extended collimator 120 mm diameter.

The experiments utilized a 20 × 20 x 20 cm rectangular water phantom that simulated a human head as clinical studies for malignant brain tumors and head-and-neck cancers are planned. The phantom was made of polymethyl methacrylate (PMMA), with wall thicknesses of 10 mm except for the front side (beam side), which was 3 mm. The inside of the phantom can be filled with pure water, and detectors for neutrons and photons can be placed inside the phantom. Multiple thin gold (Au-197) wires 0.25 mm in diameter were set inside the phantom for the measurement of the distribution of the thermal neutron flux. The water phantom was then set at the irradiation position behind the diameter of the beam aperture.

The experiment used normal beam apertures with diameters of 120 and 150 mm. The neutron distribution for an extended collimator 120 mm in diameter was also measured. After neutron irradiation of the phantom, the radioactivity of each gold wire was measured using a Ge detector, and the fluxes were determined using the activation foil method [8].

3. RESULTS AND DISCUSSION

Fig.4(a) shows the three distributions of the thermal neutron flux on the beam axis for the normal beam aperture with diameters of 120 mm, 150 mm, and an extended collimator with a diameter of 120 mm. Fig. 4(b) shows the profiles for each relative distribution, in which the flux values at each depth were divided by the maximum value for each beam aperture.

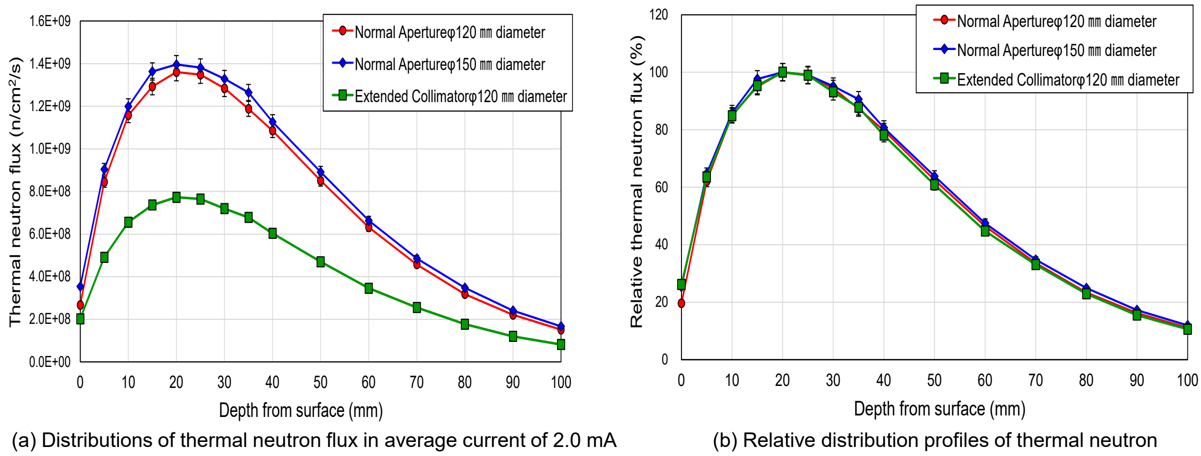


FIG. 4. Distributions of thermal neutron flux on the beam axis for each beam aperture

The maximum thermal fluxes for both normal beam apertures were 1.36 and 1.40 $\times 10^9$ (n/cm^2/s), respectively. The position of the peak was the same for all apertures; namely, 20 mm from the phantom surface on the beam axis. In the distributions for the deep direction, for the normal beam apertures, the intensity of the φ150 mm beam was only a few percent higher than that for the φ150 mm beam. However, the shape of the distribution in the deep direction was almost the same. The irradiation times were also approximately the same. Therefore, each beam aperture could be used in the same manner. For typical cases of malignant brain tumors and head and neck cancer, irradiation is expected to be completed in approximately 30 min. An appropriate beam aperture can be chosen depending on the tumor size.

The maximum thermal flux of the extended collimator was approximately 0.8×10^9 (n/cm^2/s). The intensity of the extended collimator was approximately 40% lower than that of the normal beam aperture because it protruded 10 cm from the wall. The irradiation time using the extended collimator in typical treatment cases was approximately 55 min or less. The distribution profile in the deep direction for the extended collimator was almost the same as that for the normal beam apertures. These results demonstrate that the extended collimator can be used for actual treatment as irradiation can be completed within 1 h.

4. CONCLUSIONS

The iBNCT project developed the iBNCT001, a demonstration device providing a LINAC-based neutron source that can be used for BNCT. The average current of the LINAC is currently 2.1 mA and neutrons are generated by irradiating the beryllium target with accelerated protons. The device successfully generated an epithermal neutron beam with sufficient intensity for treatment. To conduct clinical studies in the near future, the physical characteristics of the neutron beam of the iBNCT001 were assessed and several neutron irradiation experiments were performed. The neutron irradiation experiments were performed using a water phantom simulating a human head. The experimental results, in combination with the normal beam apertures, demonstrated that high-intensity thermal neutrons can be generated in the human body. Using normal beam apertures, irradiation was completed in half an hour. The application of an extended collimator created a space between the patient and the wall around the beam aperture; thus, the patient can receive irradiation while maintaining a comfortable posture, thus potentially improving irradiation accuracy. Based on the physical measurement findings, non-clinical studies are currently being performed using mouse irradiation to confirm the biological characteristics of the beam. We plan to conduct clinical studies with actual patients as soon as possible after these physical measurements and biological experiments.

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