Development of LINAC-Based Neutron Source for Boron Neutron Capture Therapy in University of Tsukuba*)

Hiroaki KUMADA, Fujio NAITO[1], Kazuo HASEGAWA[2], Hitoshi KOBAYASHI[1],
Toshikazu KURIHARA[1], Kenta TAKADA, Takahiro ONISHI, Hideyuki SAKURAI,
Akira MATSUMURA and Takeji SAKAE

Faculty of Medicine, University of Tsukuba, Tsukuba, Ibaraki 305-8575, Japan
[1]*High Energy Accelerator Research Organization, Tsukuba, Ibaraki 305-0801, Japan*
[2]*J-PARC Center, Japan Atomic Energy Agency, Tokai, Ibaraki 319-1195, Japan*

Clinical trials of the boron neutron capture therapy (BNCT) have been conducted using research reactors. Recent progresses in the accelerator and accelerator-driven-neutron-source technologies have rendered it possible to generate the substantial number of neutrons required for BNCT treatment, using a compact accelerator, which can be installed in a hospital. The University of Tsukuba launched a project for the development of a compact accelerator-based neutron source for BNCT. For this accelerator, we employed a linear particle accelerator (linac) and the energy of the proton beam was 8 MeV. Beryllium was selected as the neutron target material. To generate sufficient neutron intensity by the reaction between 8 MeV protons and beryllium, the linac accelerates a high current of 5 mA or more. As the target system is critical, we developed a beryllium target system with a three-layered structure to avoid target breakage, caused by massive heat load and blistering, within a short period. The linac-based neutron source for the BNCT is almost complete and we succeeded in generating neutrons, in 2015. Currently, several characteristic measurements are being carried out.

1. Introduction

Boron neutron capture therapy (BNCT) is a next-generation particle radiotherapy against intractable cancer such as malignant brain tumors [1]. BNCT is a binary system, based on the nuclear reaction between low-energy neutrons and isotope boron-10 accumulated in the tumor cells. Two high-LET particles such as helium-4 and lithium-7 are emitted in each tumor cell by the reaction. The ranges for both particles in the tissue are less than 10 μm, which is comparable to the size of a typical tumor cell. Therefore, invasive tumor cells infiltrating the healthy tissue can be destroyed by both particles, selectively, without critical damage to healthy tissues [2]. Figure 1 shows the principle of BNCT. This treatment requires high-intensity neutrons. Thus far, clinical trials for BNCT have been performed using research reactors. In Japan, BNCT facilities have been installed in the Kyoto University reactor (KUR), Japan atomic research reactor No. 4 (JRR-4), etc. BNCT against malignant brain tumor has been performed since 1968 and clinical trials for melanoma were conducted in the 1980s. These trials were
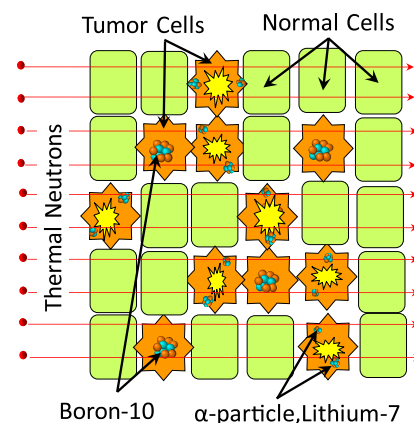

Fig. 1 Principle of BNCT.

conducted using thermal neutron beams, because several facilities for BNCT in the existing research reactors could emit only thermal neutron beams. In the clinical trial for malignant brain tumor conducted in Japan, craniotomy operation was combined with irradiation for delivering the therapeutic dose to the diseased region. Thus, BNCT research reactors in Japan had a surgical operation room with minimal apparatus for craniotomy operation.

By the end of the 20th century, some BNCT facilities were modified to generate epithermal neutron beams (0.5 eV < Energy < 10 keV) that can deliver therapeutic doses to the deeper regions within the body; hence, clinical trials were conducted using these beams. Technological innovations such as epithermal-neutron-beam irradiation contributed to the further progress of BNCT. As craniotomy in irradiation was no longer required in BNCT for malignant brain tumors, the load on patients was drastically reduced and the extensive application of BNCT was promoted. The first clinical trial for head-and-neck cancer was performed at KUR in 2001. Moreover, clinical trials for malignant mesothelioma, lung, and liver cancers were conducted using epithermal neutron beams at KUR. The application of epithermal neutron beams and the increased application for target cancer led to a drastic increase in the number of clinical trials for BNCT; clinical studies of 800 or more cases have been conducted using research reactors, in Japan, thus far. In the University of Tsukuba, the neurosurgery group conducted the first BNCT trial for malignant brain tumor using JRR-4 in 1999 [3] and subsequently, approximately 30 cases of malignant brain tumor have been treated at JRR-4. The results obtained from the trials validated the effectiveness of BNCT for intractable cancer [4]. However, the therapy has not become widespread, although its effectiveness was demonstrated. In Japan, it is impossible to build a new reactor in future due to recent environmental concerns regarding nuclear activities; therefore, reactor-based treatment facilities cannot acquire licenses for pharmaceutical use because it is no longer possible to commercialize the device. Meanwhile, the recent progresses in accelerator and accelerator-driven-neutron source technologies renders it possible to generate sufficient neutrons for BNCT treatment using compact accelerators, which can be installed in hospitals. Hence, it is expected that BNCT can be established as a general treatment, which can be received at a hospital, in the near future.

Several development projects for compact accelerator-based neutron sources, for BNCT, are being undertaken [5]. In Japan, in particular, various types of commercial devices are being produced, some of which have already succeeded in generating neutron beams. The most advanced project is the production of a cyclotron-based treatment device by Sumitomo Heavy Industries Co. (SHI). SHI has completed the production of a cyclotron-based neutron source in 2009, in collaboration with the BNCT team in Kyoto University [6]. The treatment device has been installed in two institutes: the Kyoto University research reactor institute (KURRI) in the Osaka prefecture and in the Southern Tohoku BNCT research center in the Fukushima prefecture. Currently, clinical tests for pharmaceutical approval for malignant brain tumor and head-and-neck cancer are being conducted using the device in both institutes. Furthermore, a third facility for the SHI treatment device is being constructed at Osaka medical college.

In view of the above, the University of Tsukuba had launched a project for the development of accelerator-based BNCT treatment to establish and popularize BNCT. To accomplish this goal, we set up an industry-academia-government collaboration team consisting of the University of Tsukuba, the high-energy accelerator research organization (KEK), the Japan atomic energy agency (JAEA), Hokkaido University, Ibaraki prefecture Toshiba Co., and the Mitsubishi heavy industry Co. (MHI). The team launched an R&D project named "iBNCT project" for developing an accelerator-based neutron source device applicable for BNCT.

2. Development of Accelerator-Based Neutron Source for BNCT in the iBNCT Project

2.1 Requirement of the neutron source for BNCT

For BNCT, the neutron source should generate high-intensity epithermal neutrons at the beam aperture; contaminations in the fast and thermal neutrons, and in the gamma-ray in the beam should be as low as possible. The recommended values for the neutron beam applicable for BNCT are indicated in the IAEA technical documentation [7]. Important items and their values are listed in Table 1.

To obtain the recommended epithermal neutron intensity for BNCT at the beam aperture using an accelerator-based neutron source, it is necessary to generate a neutron flux of approximately 5×10^{13} (n/cm^2/s) or more by the reaction between the proton beam and the target material, although the neutron intensity at the beam aperture depends upon the beam-shaping assembly (BSA) design or the neutron energy from the target material. The characteristics of neutrons emitted from the target material differ, depending upon the target material and the proton energy incident on the material. As the target material for an accelerator-based neutron source for BNCT, beryllium or lithium is generally applied. However, the combination of the target material and the proton energy incident on the target has

Table 1 IAEA-TECDOC recommended items and their values for the BNCT neutron beam.

Epithermal neutron flux	> 1× 10^9 n/cm^2/s
Contamination of the fast neutron	< 2×10^{-13} Gycm^2/n
Contamination of the gamma-ray dose	< 2×10^{-13} Gycm^2/n
Ratio of the thermal neutron flux and the epithermal neutron flux	< 0.05

not yet been optimized. Thus, there are several approaches for accelerator-based neutron sources, for BNCT [5].

The properties of each neutron target material are presented in brief. Lithium can efficiently emit neutrons by bombarding with an approximately 2.5 MeV proton beam, because it has a resonance peak of cross-section at around 2.5 MeV. However, lithium may melt owing to the massive heat load with high current proton irradiation as approximately a few MW/m^2 because of its low melting point at 180°C. Therefore, a lithium-based target system should exist at a sufficiently lower temperature than the melting point.

In addition, with proton irradiation, lithium changes into beryllium-7, which is a radioactive isotope with a half-life of 53 days. On the other hand, beryllium is relatively stable against a high-heat load as approximately a few tens of MW/m^2 because its melting point (1287°C) is higher than that of lithium. However, if a proton beam of more than 13.4 MeV is applied for irradiation, beryllium changes into radioisotope Be-7. In addition, several materials in the treatment device become radioactive on reacting with the high-energy neutrons released from the target material.

To generate sufficient neutron intensity for BNCT at the target material, as described above, the proton accelerator must accelerate an extremely high current of a few to a several tens of mA. With respect to the energy range of the proton beam, the protons should be accelerated from 2.5 MeV (with a lithium target) to several tens of MeV (with a beryllium target).

2.2 Concept of the University of Tsukuba's neutron source

Based on the BNCT-neutron-source requirements described above, in the iBNCT project, the specifications for the accelerator and the demonstrator target material of the BNCT accelerator-based neutron source were decided as follows [8].

First, we chose to employ beryllium as the neutron target material because beryllium has several advantages as a neutron target for a BNCT neutron source compared to lithium. Additionally, its practicality and stability for a BNCT neutron source had been proven by SHI [6]. Next, the proton beam energy was decided. If a beryllium target is used, the neutron yield depends upon the proton energy incident on beryllium; hence, a high-energy proton beam can be used to efficiently generate neutrons. However, as the reaction between the high-energy protons and beryllium emits high-energy neutrons, radiation is activated in the device and the contamination rate of the neutrons in the neutron beam is increased. Therefore, for reducing the device radiation-activation and neutron contamination, it is better to irradiate proton beams with as low energy as possible for a beryllium target. Based on the results of several investigations and analyses in the conceptual design stage,

Table 2   Specification of the neutron source for iBNCT.

Accelerator type	RFQ+DTL proton linac
Proton energy	8 MeV
Ave. proton current	> 5 mA (Max. 10 mA)
Peak beam current	Max. 50 mA
Pulse width	Max. 1 millisecond
Pulse repetition rate	Max. 200 pps
Duty	20%
Beam Power	> 40 kW (Max. 80 kW)
Target material	Beryllium
Accelerator size	< 8 m

the proton energy of our neutron source with a beryllium target was set to 8 MeV. The neutron energy emitted by the reaction with a beryllium target is 6.1 MeV or less, which is relatively lower than the precedent device using a beryllium target. For instance, the threshold for the activation of beryllium is approximately 13 MeV. For lead, which is generally used as a gamma shield, the threshold energy for the (n, 2n) reaction is approximately 8 MeV. In the case of iron, which is used as a fast neutron filter material, the threshold energy for the (n, 2n) reaction is higher than 10 MeV. These materials are generally used in the BSA of the BNCT device. Therefore, the combination of the 8-MeV proton beam and beryllium can prevent the BNCT device from becoming radioactive.

Next, we decided the proton-beam current. The results of analyses in the conceptual design stage indicated that a high current of a few mA is required to generate sufficient neutrons for BNCT by irradiating 8 MeV protons on beryllium. Therefore, the average proton current of the linear particle accelerator (linac) was set to over 5 mA (maximum: 10 mA). Thus, the proton power irradiated on the beryllium target was 40 kW or more (maximum: 80 kW). For the accelerator, we decided to use a linac system, which can generate and accelerate high-current protons. Some of the demonstrator specifications for the accelerator-based neutron source in the iBNCT project are shown in Table 2.

2.3 Development of the linac

To generate and accelerate a high-current proton beam, a radio-frequency quadrupole (RFQ) linac and a drift-tube linac (DTL)-type linac were selected as the proton accelerators. Figure 2 shows the schematic of the iBNCT accelerator-based neutron source. The accelerator consists of an ion-source such as the RFQ, DTL, etc. For the ion-source, a multicusp-type was employed because it generates an extremely high current of several tens of mA. The RFQ and DTL were designed and produced, based on the fundamental technologies of the Japan proton accelerator research complex (J-PARC) front-end linac. The J-PARC installed in Tokai village is a multipurpose and
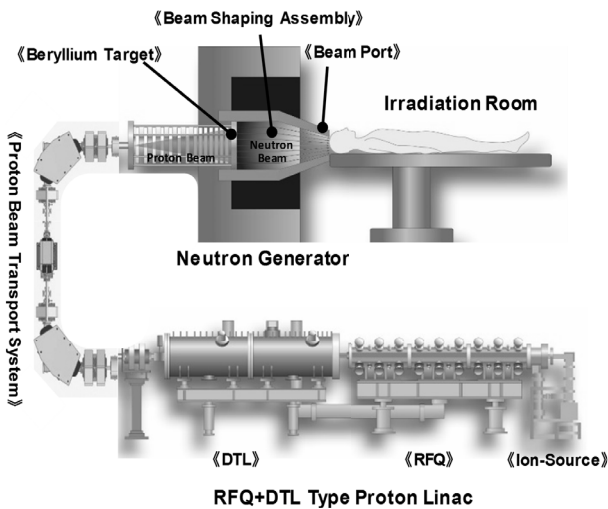
Fig. 2 Schematic of the iBNCT linac-based neutron source for BNCT.

Table 3 Details of the iBNCT linac system.

Ion-source		Multicusp type
RF system		Single 324 MHz Klystron
RFQ	Structure	4-vane type RFQ
	Injection energy	50 keV
	Output energy	3 MeV
	FR Frequency	324 MHz
	Length	3.2 m
DTL	Structure	Drift tube linac
	Injection energy	3 MeV
	Output energy	8 MeV
	FR Frequency	324 MHz
	Number of cell	31
	DT type	Permanent Magnet
	Length	3.2 m

multidisciplinary facility with a high-intensity proton accelerator device. The same type of klystron as that in the J-PARC was applied, where one klystron drives both the accelerator tubes. The iBNCT-linac-system specifications are listed in Table 3.

Protons of several tens of mA, generated at the ion-source enter the RFQ, where the low-energy protons (∼50 keV) are accelerated to 3 MeV. The beam pulse width is approximately 1 μs and the maximum repetition rate is 200 Hz. The velocity of the protons from the RFQ is further increased by the DTL and the final output energy is 8 MeV. The total length of the linac system is approximately 8 m and diameter is less than 1.5 m. This system was designed mainly by the KEK group and was manufactured by MHI. Both the RFQ and DLT tubes were completed in 2012. Figure 3 shows the actual linac tubes installed in an accelerator room in the iBNCT facility.
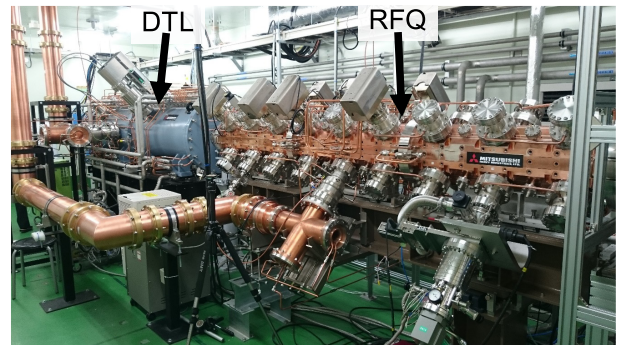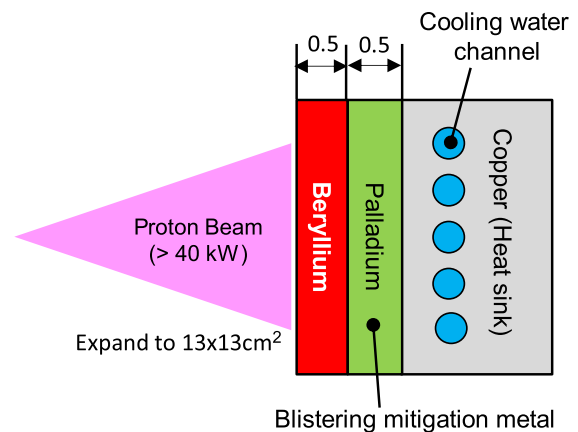

Fig. 3 Linac tubes installed in the accelerator room.

Fig. 4 Schematic of the target system with a three-layered structure.

2.4 Development of the beryllium target system

In the compact accelerator-based neutron source for BNCT, the development of a neutron target system, which can generate neutrons by reacting with the protons, is critical. In this section, the development of the beryllium target system for the iBNCT device is discussed.

For the iBNCT project, the energy and average current of the proton beam irradiating beryllium were selected as 8 MeV and over 5 mA, respectively, as described above. Thus, an extremely-high power of 40 kW or more (maximum 80 kW) is injected to beryllium. Therefore, the beryllium target system had two developmental issues. The first is to suppress the breakage and degradation of the target system within a short period due to blistering. The second is to prevent the beryllium target system from melting, owing to the massive heat load by the incident protons.

In the target-system design, we set the exchange frequency (life time) of the target unit to one year; the irradiation time with a proton beam current of 10 mA was assumed to be 250 h. In view of the above, as a countermeasure for blistering, we devised a target system with a three-layered structure consisting of a beryllium layer, a blistering mitigation layer, and a heat sink [9]. Figure 4 shows the

schematic of the target system with a three-layered structure.

Blistering is a phenomenon in which the protons stopped in the material by proton irradiation combine with the electrons in the components causing hydrogenation. The hydrogens in the components expand and finally, break the components. In particular, beryllium as a target material and copper, which is generally used as a heat sink, have low blistering resistances. Hence, a target system, which does not have countermeasures against blistering, may be broken within a short period due to hydrogen embrittlement. Thus, we designed a target structure that prevents the incident protons stopping inside beryllium. The Bragg-peak depth of proton in beryllium is approximately 0.55 mm. Therefore, the beryllium thickness of the target system was set to 0.5 mm, which is thinner than the penetration range. A plate made of palladium, which is a blistering mitigation material was placed behind the beryllium plate. The thickness of the palladium plate, as the 2nd layer, was 0.5 mm. Therefore, the incident protons generate neutrons from beryllium, while passing through the 1st beryllium layer and finally, stop at the 2nd palladium layer. By storing hydrogen in the palladium layer, which can absorb hydrogen, the breaking of the beryllium target system by blistering can be delayed. Finally, a heat sink block made of copper was installed behind the palladium plate as the 3rd layer of the target system in order to cool both the beryllium and palladium layers. The three materials were bonded with diffusion bonding, using hot isostatic pressing.

For preventing the melting of the target system, which is the second issue, several countermeasures were undertaken in the target system. To remove the heat loads of both the beryllium and palladium layers, a cooling water channel was installed within the copper heat-sink block. By circulating cooling water at flow rate of 50 L/min and at a high-speed of 10 m/s through the cooling-water channel, the heat in the target system was transferred to the nucleate boiling region, avoiding catastrophic boiling. Furthermore, to the reduce the heat load against the beryllium layer, the proton beam profile irradiating the beryllium target was expanded to a 13-cm × 13-cm rectangular area using two quadrupole and two octapole electromagnets. If the input to the beryllium layer is 80 kW, as the maximum power of the linac, the heat-load density of the beryllium surface is dispersed to 4.5 MW/m² or less. The value of heat-load density is a sufficiently low value for the melting of beryllium. And to prevent breakage in the beryllium target by problems in the proton-beam expansion, certain interlocks were installed in the accelerator control system with detectors, for heat distribution on the target layer, the temperature of the cooling water, etc. We have completed the production of the beryllium-based target system with a three-layered structure, involving several countermeasures, as the key technology of the iBNCT-device neutron source.
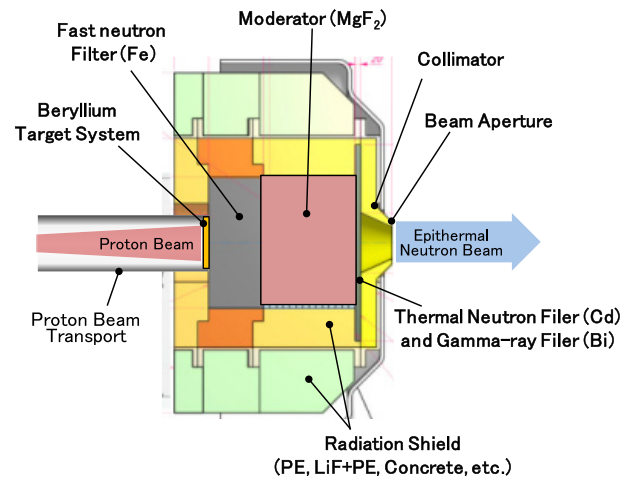

Fig. 5   Cross-sectional view of the iBNCT-device BSA.

2.5   Design of the beam-shaping assembly

The high-energy neutrons emitted from the beryllium target system must be shaped as a neutron beam suitable for irradiating the human body safely to realize BNCT treatment. Thus, the BSA of the neutron generator was optimally designed. Figure 5 shows the cross-sectional view of the BSA.

The BSA consists of a fast neutron filter, a thermal neutron filter, a moderator, a gamma-ray filter, a collimator, radiation shields, etc. First, the neutrons (< 6.1 MeV) generated from beryllium are removed using the fast neutron filter made of iron. The filter is installed behind the copper heat sink of the beryllium target system. Next, the energy of the filtered neutrons is further reduced by a moderator made of magnesium fluoride. Further, the low-energy neutrons (< 0.5 eV) are cut-off by the thermal neutron cadmium filter made of cadmium. And the gamma-ray generated by the reaction of the neutrons with several materials is reduced by the gamma-ray filter made of bismuth. Both the filters are located behind the moderator. Finally, the epithermal neutrons are focused and delivered into the beam aperture by a collimator installed at the end of the BSA. The collimator is formed mainly with blocks made of polyethylene mixed with lithium fluoride (PE + LiF). To suppress radiation-exposure for a patient during irradiation, the leakage radiation from the outside wall of the beam aperture must be as low as possible. Hence, the BSA is structured to enclose the neutron delivery part consisting of the moderator and collimator with several shielding components. LiF, lead and concrete, etc. were used for shielding. Each material was installed at a suitable location to effectively inhibit both neutrons and gamma-rays.

3. Beam Performance of the iBNCT Device

The linac-based neutron source was constructed by the end of 2015, and commissioning and conditioning began in
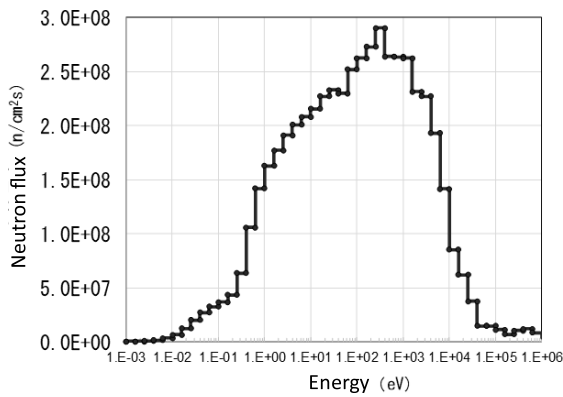
Fig. 6   Neutron spectrum at the beam aperture of the iBNCT device.

2016. Several improvements and modifications were carried out to generate a high current of a few mA. To confirm the characteristics of the neutrons generated by the device, neutron-spectrum measurements were performed using the Bonner sphere method, under a free-in-air condition with a low beam current. The experimental results demonstrated that the device emits epithermal neutrons applicable for BNCT and that the spectrum of the actual beam is comparable to that expected in the design stage [10]. Figure 6 shows the neutron spectrum at the beam aperture, where the neutron intensity is normalized to an average proton current of 5 mA.

In 2017, the device could generate sufficient neutrons, while driving the accelerator with a high proton current of a few mA. Currently, we are performing several measurements to verify the neutron characteristics for applicability to actual treatment and for ensuring the safety of a living body. To establish the degradation characteristics and lifetime and of the beryllium target unit, it is intended to perform long-time operation with repeatedly neutron generation and determine the exchange frequency of the unit.

4. Conclusions

To establish BNCT as a general treatment that can be performed in a hospital, compact accelerator-based neutron sources are being developed around the world. The neutron source for BNCT must emit an epithermal neutron flux of 1×10^9 (n/cm^2/s) or more at the beam aperture. Hence, it is necessary to generate 5×10^{13} (n/cm^2/s) or more neutron flux at the neutron target point. Therefore, the BNCT accelerator should drive with a high-current of a few mA or more. For the neutron target system, several countermeasures against a large heat load of several

tens of kW and the blistering caused by substantial proton irradiation must be developed. The iBNCT project team developed and fabricated an RFQ+DTL type linac-based neutron source for BNCT. The proton energy was specified as 8 MeV and beryllium was employed as the target material. The linac, which can accelerate a high current of 5 mA or more, was designed, based on the front-end-linac of J-PARC. A beryllium target system with a three-layer structure was developed as the neutron target system to prevent breakage, which is caused by heat load and blistering, within a short period. Construction of the accelerator was completed by the end of 2015, and commissioning and improvements are being undertaken at present. The accelerator has already succeeded in driving with an average proton current of approximately 1 mA, and neutrons with sufficient intensity for BNCT treatment have been generated. Currently, the characteristic measurements of the neutron beam are under progress. Measurement results, using the Bonner sphere method, demonstrated that the device can produce an epithermal neutron beam per design. We intend to carry out a few more physical measurements, including the life-time estimation of the target unit. Further, biological experiments, such as cell irradiation and small-animal irradiation, to confirm the applicability and safety of the neutron beam for actual BNCT treatment, are being conducted. Based on the results of the non-clinical tests, we expect to perform clinical trials using our linac-based neutron source.

Acknowledgments

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