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Accelerator based epithermal neutron source for clinical boron neutron capture therapy

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Abstract. The world's first accelerator based epithermal neutron source for clinical boron neutron capture therapy (BNCT) was designed, developed, and commissioned between 2008 and 2010 by Sumitomo Heavy Industries in collaboration with Kyoto University at the Kyoto University Institute for Integrated Radiation and Nuclear Science. The accelerator system is cyclotron-based and accelerates a proton up to an energy of approximately 30 MeV. The proton strikes a beryllium target, which produces fast neutrons that traverse a beam shaping assembly composed of a combination of lead, iron, aluminum, and calcium fluoride to reduce the neutron energy down to the epithermal range (∼10 keV) suitable for BNCT. The system is designed to produce an epithermal neutron flux of up to 1.4×10^9 n · cm^{-2} · s^{-1} (exiting from the moderator of a 12 cm diameter collimator) with a proton current of 1 mA.

In 2017, the same type of accelerator was installed at the Kansai BNCT Medical Center and in March 2020 the system received medical device approval in Japan (Sumitomo Heavy Industries, NeuCure® BNCT system). Soon after, BNCT for unresectable, locally advanced, and recurrent carcinoma of the head and neck region was approved by the Japanese government for reimbursement covered by the national health insurance system.

Keywords: BNCT, Cyclotron, neutron detection, Monte Carlo simulation, commissioning

1. Introduction

Boron neutron capture therapy (BNCT) is a binary radiotherapeutic treatment modality based on the nuclear reaction that occurs when a ^{10}B atom captures a thermal neutron generating high LET particles. These particles deposit their energy over a short range (several μm), which is on the order of the diameter of a typical human cell [12]. Recently, there has been significant development in accelerators-based neutron sources (ABNS) and there are several countries that have developed or are currently developing an ABNS for BNCT [9,10]. The world's first commercially available ABNS for clinical BNCT was developed by Sumitomo Heavy Industries (NeuCure® BNCT system) with the system obtaining approval of a new medical device for manufacturing and sales from the Japanese Ministry of Health, Labor, and Welfare in March 2020. In June 2020, BNCT for the treatment of unresectable, locally advanced, and recurrent carcinoma of the head and neck cancer has been approved by the Japanese government for reimbursement under the national health insurance.

The NeuCure® BNCT system was installed at the Kansai BNCT Medical Center in the Osaka Medical and Pharmaceutical University, shown in Fig. 1. This is the world's first center to offer insurance covered BNCT at a university hospital. The accelerator system is a cyclotron and accelerates a proton up to an energy of approximately 30 MeV. The accelerated proton strikes a beryllium target, which produces fast neurons that traverse a beam

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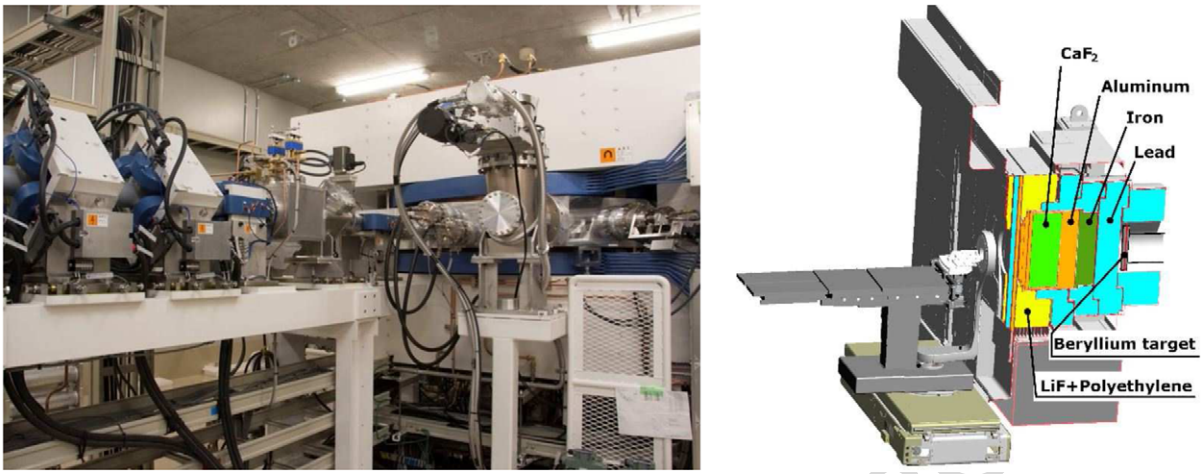

Fig. 1. Image of the NeuCure® BNCT system (cyclotron) and a cross-sectional diagram of the beam shaping assembly.

shaping assembly to reduce the energy down to the epithermal energy range suitable for clinical BNCT. This paper describes the beam characterisation tests performed at the Kansai BNCT Medical center as part of the clinical commissioning of the system.

2. Material and methods

2.1. NeuCure® BNCT system: Beam characteristics

2.1.1. Cyclotron-based epithermal neutron source beam model

The system installed at the Kansai BNCT Medical Center is the same type as the one installed at the Kyoto University Institute for Integrated Radiation and Nuclear Science [11,15]. The fast neutrons generated from the Be target traverse through a carefully designed beam shaping assembly (BSA) to reduce the neutron energy to approximately few tens of keV, which has been shown to be an effective energy for deep-seated tumours [16]. The simulation of the neutron and gamma ray distribution was performed using a general-purpose Monte Carlo particle transport simulation code system (Particle and Heavy Ion Transport code System: PHITS version 3.24 [14]). The parameters were evaluated in-air for a 12 cm diameter collimator at the collimator exit. The neutron energy range was defined as $0 - 5 \times 10^{-2}$ eV (thermal), 5×10^{-2} eV-10 keV (epithermal), and 10 keV-30 MeV (fast). Detail on the beam modelling and source information can be found elsewhere [5].

2.1.2. Neutron flux determination

A common method for measuring the neutron spectrum is metal activation, with gold and indium being frequently used for the measurement of thermal and fast neutrons, respectively. An acrylic phantom filled with distilled water was used, shown in Fig. 2. A 10 cm long gold wire (diameter of 0.25 mm with a 99.95% purity, The Nilaco Corporation) was placed along the central axis of the beam. As gold reacts to both thermal and epithermal neutrons, measurements were performed with and without a cadmium cover to shield the thermal neutrons. A total of 0.3 C for the gold wire and 0.6 C for the gold wire with cadmium cover was delivered. After irradiation, the gold wire was cut into small pieces (approximately 5 mm in length) and the gamma rays emitted from the activated gold was measured using a germanium detector.

The reaction rate per unit charge of the gold sample was calculated using the expression below.

$$R = \frac{\lambda N}{\epsilon \gamma e^{-\lambda T_C}(1 - e^{-\lambda T_m}) \sum_{i=1}^{n} (\frac{Q_i}{\Delta t}(1 - e^{-\lambda \Delta t}) e^{-\lambda (n-i)\Delta t})}$$

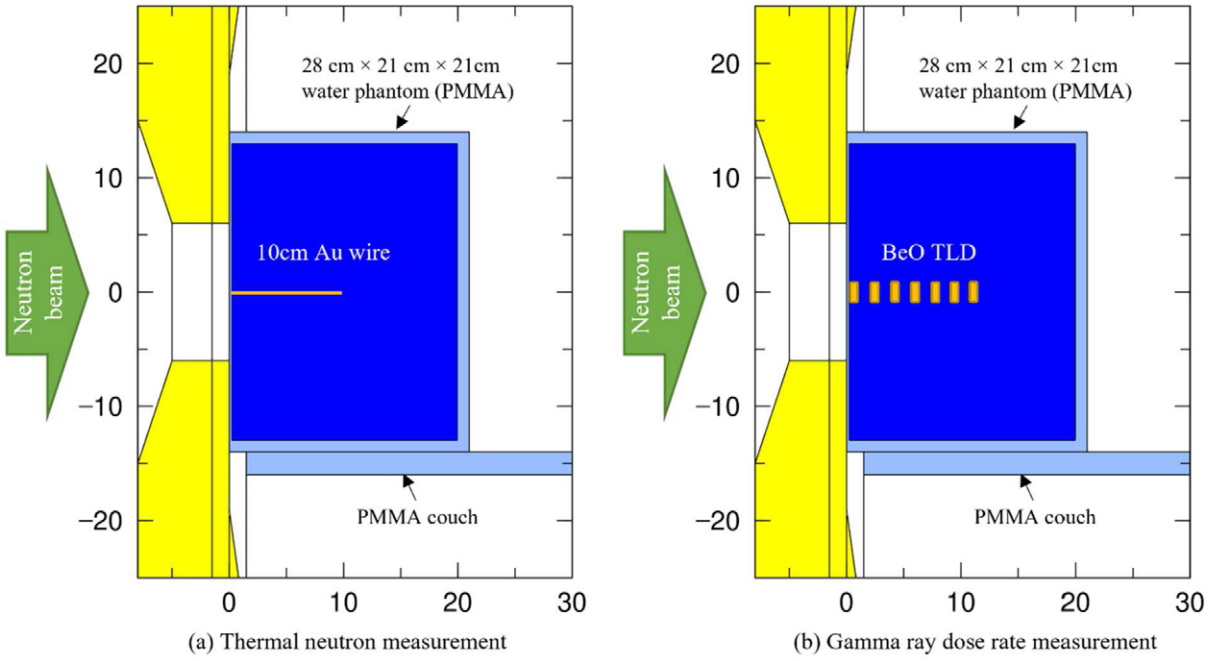

Fig. 2. Diagram of the water phantum used for the determination of the (a) thermal neutron and (b) gamma ray distribution.

Where ϵ is the detection efficiency of the detector of the gamma rays emitted from ^{198}Au, γ is the gamma ray emission rate from ^{198}Au decay, λ is the decay constant of ^{198}Au, T_c is the time from the irradiation to the start of the measurement, T_m is the measurement time, N is the peak count due to the detector measured gamma rays emitted from ^{198}Au and Q_i is the electric charge irradiated on the target at each interval, Δt.

For the measurement of fast neutrons, indium foil was used (diameter of 3 mm with a thickness of 0.1 mm with a 99.99% purity, The Nilaco Corporation). ^{115}In (natural abundance of 95.7%) is excited by the (n, n') process producing ^{115m}In, which returns to the ground state by emitting a 340 keV gamma ray. The threshold neutron energy of this nuclear reaction is approximately 340 keV [7].Indium also reacts to thermal neutrons that produce both beta and gamma rays with different energies, making the measurement of the 340 keV difficult. To minimise these reactions, the indium foil was covered with cadmium to shield the low energy neutrons. The cadmium covered indium foil was placed at the surface, 1 cm, 2 cm, and 6 cm depth inside the water phantom along the central axis. A total proton charge of 3.6 C was delivered. After irradiation, the activation was measured using the same method as above.

2.1.3. Gamma ray dose rate determination

For the measurement of gamma ray dose, thermo-luminescent dosimeters (TLDs) were used. Commercially available BeO powder TLD is usually encapsulated in borosilicate glass, which has a high sensitivity to thermal neutrons. Therefore, a special ordered BeO TLD enclosed in a quartz glass capsule (which has low sensitivity to thermal neutrons) was used to measure the gamma ray dose rate in the phantom. This TLD has been used previously by Sakurai et al. at the Kyoto University Research Reactor [13] and was calibrated using a ^{60}Co source. The TLDs used in this study were calibrated using a high energy 4 MV linear accelerator.

Table 1
NeuCure® BNCT system beam properties evaluated free-in-air at the beam exit of a 12 cm diameter collimator

Parameter	Desired value*	Evaluated value
Epithermal neutron flux ($n \cdot cm^{-2} \cdot s^{-1}$)	$>1.0 \times 10^{9}$	7.0×10^{8}
Fast neutron dose ($Gy \cdot cm^{2}$)	$<2.0 \times 10^{-13}$	6.6×10^{-13}
Gamma ray dose ($Gy \cdot cm^{2}$)	$<2.0 \times 10^{-13}$	1.2×10^{-13}
Thermal / epithermal ratio	$<5.0 \times 10^{-2}$	2.7×10^{-2}
Current / flux ratio	$>7.0 \times 10^{-1}$	7.9×10^{-1}

*IAEA TecDoc 1223

2.2. NeuCure® BNCT system: Clinical characteristics

To calculate the total dose delivered to a patient, first the absorbed dose D_x arising from the reaction between a neutron and each atom inside the patient must be determined. The absorbed dose is calculated as follows:

$$D_x = \int \varphi(E) K_x(E)\, dE$$

where $\varphi(E)$ is the neutron/photon fluence (cm^{-2}), $K(E)$ is the KERMA coefficient, and the subscript x denotes the element. The total dose delivered to a patient receiving BNCT is calculated by multiplying the absorbed dose of each individual radiation component present in the field with the corresponding relative biological effectiveness (RBE) and taking the sum.

$$D_T = CBE \times D_B + RBE_H \times D_H + RBE_N \times D_N + RBE_\gamma \times D_\gamma$$

where D_T represents the total absorbed dose from each component, D_B is dose resulting from the ^{10}B (n, α)^{7}Li reaction, D_H is the dose from the epithermal and fast neutrons causing reoil protons from hydrogen in tissue, D_N is the dose from the ^{14}N in tissue capturing a thermal neutron and emitting a proton in a ^{14}N(n, p)^{14}C reaction, and D_γ is dose from the gamma rays accompanying the neutron beam as well as gamma rays induced in the tissue itself. RBE_H, RBE_N and RBE_γ are relative biological effectiveness (RBE) values of hydrogen, nitrogen, and gamma rays, respectively. The compound biological effectiveness (CBE) is defined as the product of the RBE of the short-range alpha and lithium particles and the boron distribution.

The central axis RBE weighted dose distribution inside a homogeneous cubic phantom (20 cm ×20 cm×20 cm) was calculated using PHITS. The phantom material was set to soft tissue ICRU 4 component, with the ^{10}B concentration set to 25 μg/g spread out uniformly. The tumour CBE and tumour to healthy tissue ratio was set to 3.8 and 3.5, respectively. The healthy tissue CBE was set to 1.34 and the RBE for the nitrogen and hydrogen component was set to 2.9 and 2.4, respectively. For the calculation of the skin dose, the phantom material composition was set to ICRU 44 skin with a physical density of 1.09. The healthy skin CBE was set to 2.5. These parameters were taken from previous studies [1–4].

3. Results and discussion

The simulated beam parameters evaluated in air for a 12 cm diameter collimator is summarised in Table 1, along with the recommended values by the IAEA [6]. The epithermal flux and fast neutron component of this accelerator system was found to be outside the desired values recommended by the IAEA. It is worthwhile to note that these recommended values are based on nuclear reactors and not accelerator type neutron sources. Also, the location and region where these parameters are ought to be evaluated is not clearly stated. A new set of recommended values applicable for accelerator type BNCT neutron sources may be necessary.

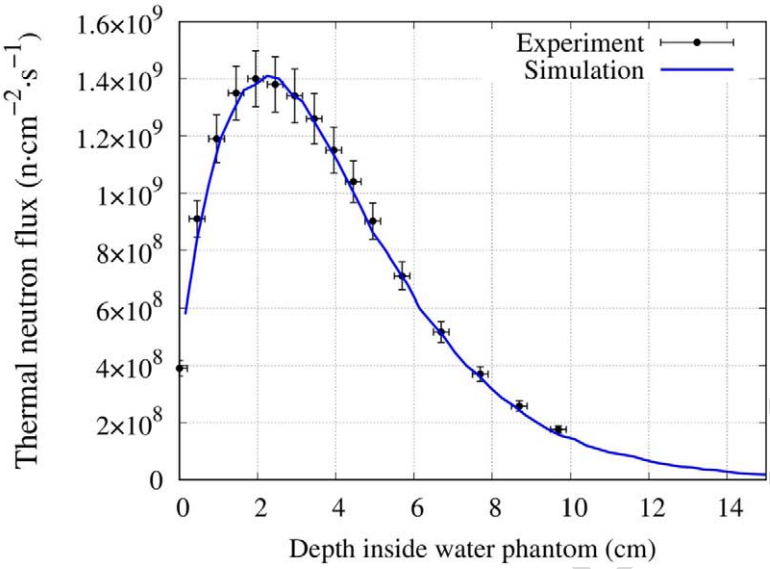

Fig. 3. Thermal neutron distribution along the beam central axis for the 12 cm diameter collimator.

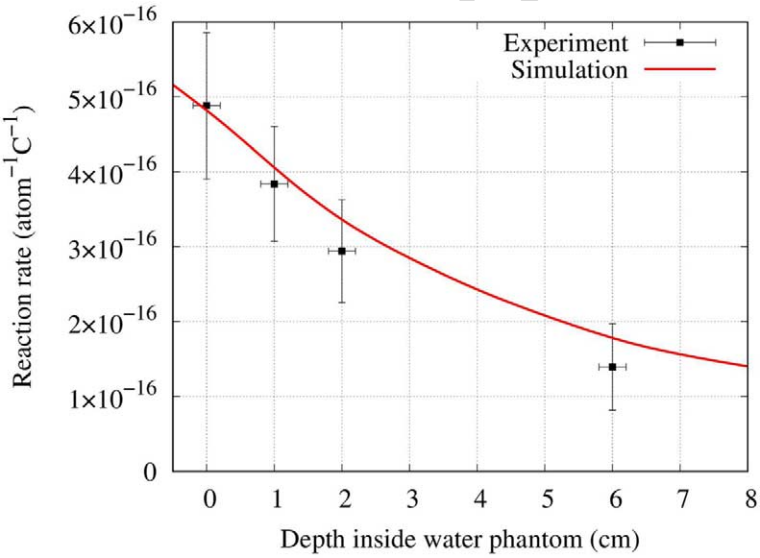

Fig. 4. Fast neutron distribution along the beam central axis for the 15 cm diameter collimator.

The thermal neutron and fast neutron distribution along the central beam axis are shown in Fig. 3 and Fig. 4, respectively. The simulation results closely matched the experimentally determined values. For the 12 cm diameter circular collimator, the peak of the thermal neutron flux inside the water phantom occurred at a depth of around 2 cm with a value of 1.4×10^9 n $\cdot$ cm^{-2} $\cdot$ s^{-1}.

The gamma ray dose rate along the central beam axis for the 12 cm diameter circular collimator is shown in Fig. 5. The distribution closely resembled the thermal neutron distribution, which indicated most gamma rays detected inside the water phantom was due to the ^{1}H(n, γ)^{2}H reaction.

The simulated central axis dose distribution of the NeuCure® BNCT system for the healthy tissue and tumour for

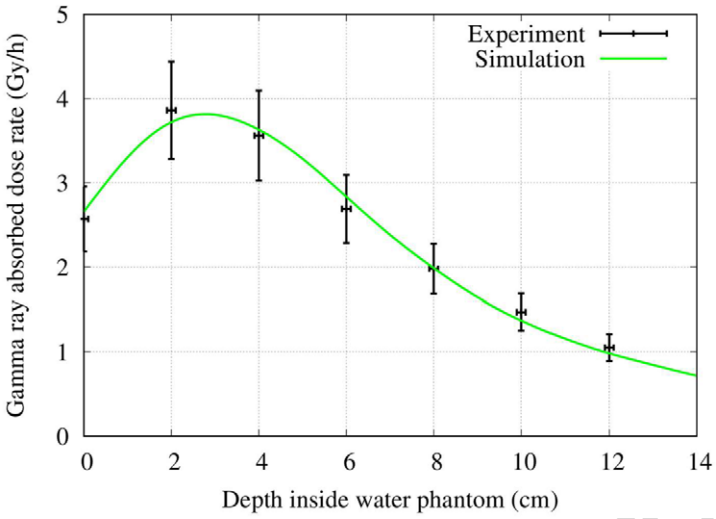

Fig. 5. Gamma ray dose rate distribution along the beam central axis for the 12 cm diameter collimator.

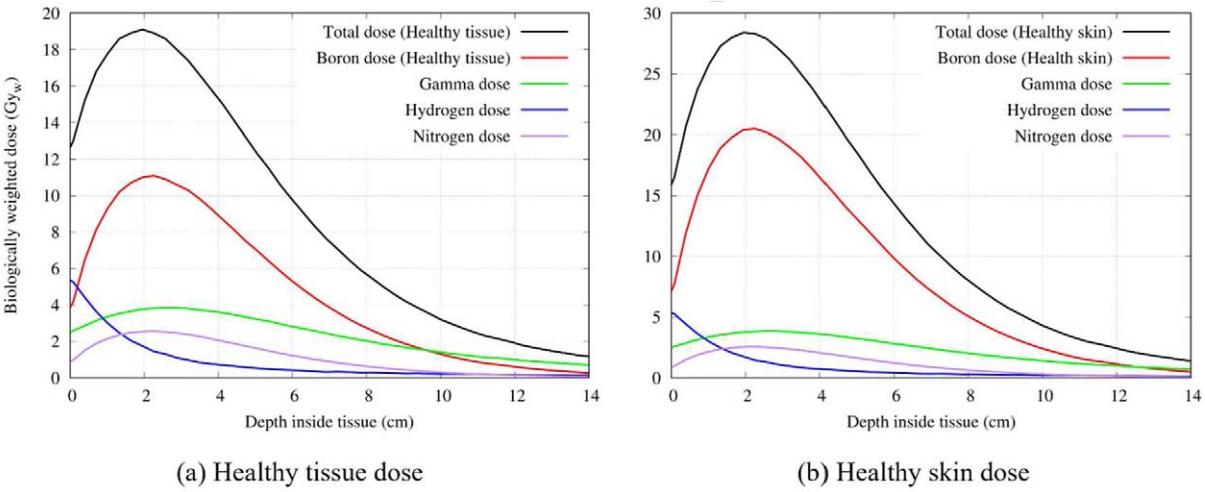

Fig. 6. The total biologically weighted dose along the central beam axis of the NeuCure® BNCT system for an irradiation time of 1 hour for (a) healthy tissue, and (b) healthy skin.

a 1-hour irradiation is shown in Fig. 6 and Fig. 7, respectively. The dominant dose component was the boron dose (resulting from the alpha particle and ^{7}Li ion), with the effect being more distinct for the tumour dose (>90%). Normally, for BNCT the dose is prescribed to the healthy tissue (e.g., skin, brain, or mucosal membrane). In a recent study performed by Kawabata et al., a dose of 8.5 Gy-Eq was prescribed to the skin scalp [8]. Using the same prescription, this system will deliver 8.5 Gy-Eq to the skin scalp in approximately 30 minutes, which is below the reasonable treatment time mentioned in the IAEA technical report (1 hour).

With the relatively high fast neutron component, the dose at the surface (i.e. skin dose) needs to be carefully examined. Also, it is important to note that the boron distribution was assumed to be uniform throughout the phantom. In reality, the boron distribution is non-uniform, and the uptake varies with different tissue/tumour types.

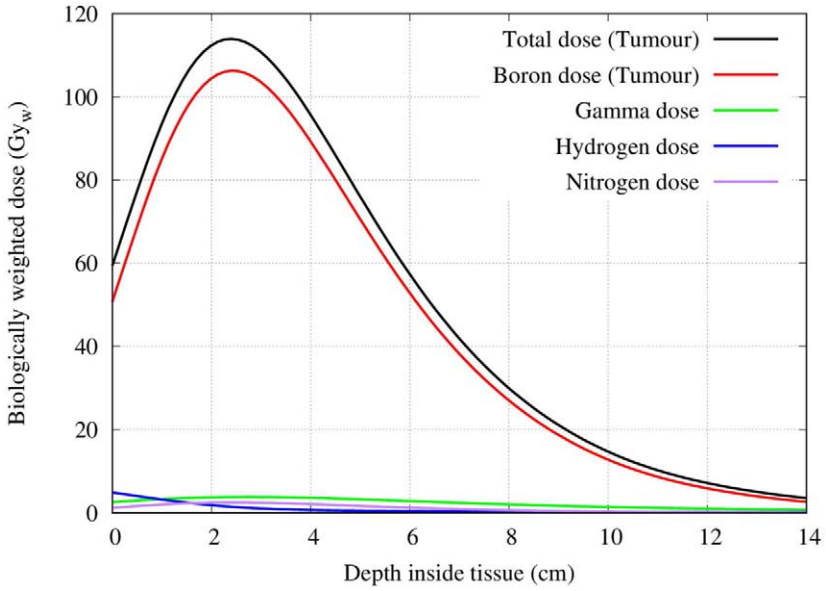

Fig. 7. The tumour total biologically weighted dose along the central beam axis of the NeuCure® BNCT system for an irradiation time of 1 hour.

4. Conclusion

The world's first clinical accelerator based epithermal neutron source developed by Sumitomo Heavy Industries was installed at the Kansai BNCT Medical Center and performance tests were undertaken to verify the system before clinical use. The neutron and gamma ray distribution inside a water phantom was verified by experimental measurements and Monte Carlo simulations. The simulated dose distribution inside a homogeneous phantom showed the dominance of the boron dose component and the system can deliver a treatment of a brain tumour below the recommended irradiation time stated in the IAEA technical report.

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