

# European Association of NeuroOncology Magazine

Neurology · Neurosurgery · Medical Oncology · Radiotherapy · Paediatric Neuro-oncology · Neuropathology · Neuroradiology · Neuroimaging · Nursing · Patient Issues

## **Boron Neutron Capture Therapy for Glioblastoma: A Phase-I/II Clinical Trial at JRR-4**

Nakai K, Yamamoto T, Kumada H

Matsumura A

*European Association of*

*NeuroOncology Magazine 2014; 4 (3)*

116-123



Homepage

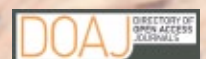
[www.kup.at/  
journals/eano/index.html](http://www.kup.at/journals/eano/index.html)

Online Database Featuring  
Author, Key Word and  
Full-Text Search



THE EUROPEAN ASSOCIATION OF  
NEUROONCOLOGY

Member of the



Indexed in EMBASE

# Boron Neutron Capture Therapy for Glioblastoma: A Phase-I/II Clinical Trial at JRR-4

Kei Nakai<sup>1</sup>, Tetsuya Yamamoto<sup>1,2</sup>, Hiroaki Kumada<sup>1,2</sup>, Akira Matsumura<sup>1</sup>

**Abstract:** Boron neutron capture therapy (BNCT) is a cell-selective radiation therapy for the treatment of glioblastoma. We reviewed the experience of our BNCT clinical trial and report the present state in 17 cases. Endpoints of our analysis were the efficacy and safety data of BNCT for newly diagnosed glioblastoma.

Adverse events seen in our patients included post-treatment brain oedema, convulsion, and diplopia due to swallowing. For newly diagnosed glioblastoma (GBM), median overall survival (OS) reached 25.7 months, and the 1- and 2-year OS rates were 85.7 % and 45.5 %, respectively. BNCT could prolong OS in selected

cases. *Eur Assoc NeuroOncol Mag* 2014; 4 (3): 116–23.

**Key words:** boron neutron capture therapy, radiation therapy, glioblastoma, efficacy, safety, adverse events

## Introduction

The first clinical trial of boron neutron capture therapy (BNCT) for brain tumours was performed in the 1950s using a research reactor in the United States [1–3]. Although glioblastoma (malignant glioma WHO grade 4; GBM) has been a candidate for BNCT for more than 60 years [4–12], BNCT for GBM has not become widely accepted for complex and diverse reasons. Over 900 patients have undergone BNCT worldwide and the radiobiological effects of BNCT on malignant tumours and normal surrounding tissue seemed to be established. However, all previous trials of BNCT for brain tumours had small patient series (Table 1) and used different treatment systems (ie, the neutron source and boron agents).

In addition, at present, the only neutron source suitable for BNCT is a nuclear research reactor. In Japan, to maintain safety standards at each nuclear reactor, the reactor must be shut down for several months each year and thus cannot be used for BNCT during that period. Research reactors require costly maintenance and adequate manpower, and the issue of nuclear fuel recycling is a worldwide problem. Moreover, the boron agents required for clinical trials are reagent products that require their own clinical trials to be certified as medical drugs.

We focused on clinical trials for glioblastoma and provide an overview of BNCT based on our BNCT experiences at the Japan Research Reactor No 4 (JRR-4) with a discussion of our new protocol and thoughts about the future of BNCT.

## Principles of BNCT

BNCT ideally damages only boron-accumulating cells. Preloaded <sup>10</sup>B, which is a non-radioactive isotope of boron, and low-energy thermal neutrons make the nuclear reaction notation <sup>10</sup>B(n, α) <sup>7</sup>Li, which releases the high linear energy transfer of α particles and <sup>7</sup>Li particles with a short path-length as cell diameter (Figure 1). Therefore, the cell-killing effect would be distributed only around the boron atoms. The

effectiveness of BNCT depends on the boron distribution and the concentration ratio between normal tissue and tumour tissue, and on the neutron-beam permeability.

## Materials and Methods

### Neutron Source: Japan Research Reactor No 4

JRR-4 is a light-water-moderated and -cooled enriched-uranium swimming pool-style reactor that uses ETR-type fuel. Modification of JRR-4 for core conversion began in 1996, and a medical irradiation facility was installed for BNCT and the reactor was adopted to generate epithermal as well as thermal beams. The BNCT facilities are a neutron beam system, which can be used with thermal and epithermal neutrons and their mix-beam, a wide irradiation room, an irradiation monitoring system, and a fully equipped operation room for craniotomies and setting simulations. The neutron beam spectrum can be changed by D<sub>2</sub>O thickness in a heavy-water tank with a cadmium shutter [4].

We started clinical BNCT trials in 1998 at JRR-4 with the thermal neutron beam [5]. In this trial (protocol II), each patient receives general anaesthesia and intraoperative neutron irradiation is performed. At the later stage of intraoperative BNCT (since 1999), we used the epithermal beam mode. The epithermal neutron beam penetrates to deeper lesions compared to the thermal beam, and it thermalises in the tissue; the use of the epithermal beam thus improved neutron distribution at deep lesions.

Received on November 1, 2013; accepted after revision on April 30, 2014; Pre-Publishing Online on May 27, 2014

From the <sup>1</sup>Department of Neurosurgery, <sup>2</sup>Department of Radiation-Oncology, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan

**Correspondence to:** Kei Nakai, MD PhD, Department of Neurosurgery, Faculty of Medicine, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan; e-mail: knakai@md.tsukuba.ac.jp

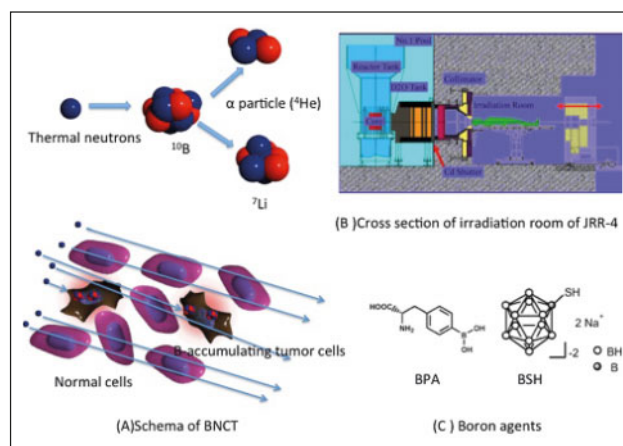


Figure 1. The concept of boron neutron capture therapy (BNCT).

**Table 1.** Clinical BNCT trials for patients with malignant brain tumours.

Reactor (Institute)	Beam	Periods	Boron agents	Pathology	n	Median survival (months)	Ref
Brookhaven Graphite Research Reactor	Thermal	1951–1959	Borax	Highly malignant brain tumour	10	3.2	[1, 3, 13]
			Sodium pentaborate iv	Highly malignant brain tumour	9	4.9	[14]
			Sodium pentaborate ia	Highly malignant brain tumour	9	3.2	
Massachusetts Institute of Technology (MIT) Reactor	Thermal	1959–1961	Carboxylphenylboronic acid	GBM (n = 16)	17	5.7	[15]
			Sodium decahydrocarborane	Medulloblastoma (n = 1)			
BMRR	Thermal	1959–1961	Sodium pentaborate	Brain tumour	18	2.9	[16]
5 Japanese reactors*	Thermal	1968–1996	BSH	Malignant brain tumour	na	GBM 21.3 AA 60.4	[17, 18]
BMRR	Epithermal	1994–1999	BPA	GBM	53	12.8	[19–22]
MIT Research Reactor	Epithermal	1996–1999	BPA	GBM	20	11.1	[23, 24]
Hugh Flux Reactor	Epithermal	1997–2002	BSH	GBM	26	10.4–13.2	[25, 26]
Finnish Research Reactor 1	Epithermal	1999–2001	BPA	GBM	30	13.4 (290 mg) 21.9 (450 mg)	[27, 28]
		2001–2008	BPA	rGBM	20	7	
KUR/JRR-4 (Osaka Medical School)	Mixed/Epithermal	1997–	BPA + BSH	GBM	21	15.6	[29–31]
			BPA	rGBM	22	10.8	
KUR/JRR-4 (Tokushima University)	Mixed/Epithermal	1998–	BSH, BSH + BPA	GBM	23	19.5	[32, 33]
JRR-4 (University of Tsukuba)	Mixed/Epithermal	1998–2011	BSH, BSH + BPA	GBM	15	25.7	[34, 35]
LVR-15 (Czech Republic)	Epithermal	2000–2002	BSH	GBM	5	na	–
Studsvik Research Reactor	Epithermal	2001–2003	BPA 900	GBM	29	14.2	[36–39]
		2001–2005	BPA 900	rGBM	12	na	–

BMRR: Brookhaven Medical Research Reactor; KUR: Kyoto University Reactor; mixed/epi: thermal and epithermal mixed-beam mode and/or epithermal beam; BPA: boronophenylalanine; BPA 900: BPA 900 mg/kg; BSH: sodium borocaptate; AA: anaplastic astrocytoma; GBM: glioblastoma; rGBM: recurrent glioblastoma

\* Hitachi Training Reactor, Japan Research Reactor No. 2, Japan Research Reactor No. 4, Musashi Institute of Technology Reactor, and Kyoto University Reactor

Using a pre-treatment simulation, we started a new protocol of non-craniotomy BNCT. However, in December 2007, a crack in a graphite reflector of the reactor core was found on a weld of the aluminium cladding. JRR-4 was stopped until February 2010 for replacement of the graphite reflector. After restarting BNCT in 2010, we treated 3 patients (with newly diagnosed GBM, recurrent GBM, and malignant meningioma, respectively) under the new protocol. Because of the March 2011 East Japan earthquake and tsunami, JRR-4 was stopped again with no prospect of restarting.

### Design of Our Clinical Trial

The BNCT protocols were approved by the Medical Ethics Committee of the University of Tsukuba, and all participat-

ing patients were fully informed and provided their written informed consent. Table 2 summarises the changes in protocol. The later stages of this trial (protocols III and IV) were registered with the Japanese authority on clinical trial registration (ie, the University Hospital Medical Information Network Clinical Trial Registry: UMIN-CTR; trial IDs: C000000298, UMIN000003984, and UMIN000003692). The concept of our clinical trial was a phase-I/II study for newly diagnosed GBM. The primary endpoints were safety and dose distribution to the tumour evaluated in GBM patients who were treated with BNCT, secondary endpoint was the survival benefit. Yamamoto et al described the details of clinical trials II and III in 2009 [6]. After the restart of JRR-4 in 2010, we started up new protocols (protocols IV and IVr) and 3 patients were treated.

**Table 2.** BNCT protocols for malignant glioma by the University of Tsukuba.

Protocol	Period	Tumour grade (WHO)	Beam	Operation	Dose estimation	Boron agents	Additional external radiotherapy	n (WHO IV/total)
I	1996–1998	III, IV	Thermal	+	Gold wire	BSH 5 g/body	–	5/9
II	1999–2002	III, IV	Epithermal	+	JCDS	BSH 5 g/body	–	2/3
III	2003–2004	IV	Epithermal	–	JCDS	BSH 5 g/body + BPA 250 mg/kg	30 Gy/15 fr	8/8
IIIr	2005–2007	IV rec	Epithermal	–	JCDS	BSH 5 g/body	–	3/3
IV	2010	IV	Epithermal	–	JCDS	BPA 250 mg/kg	40 Gy/20 fr	1/1
IVr	2010	IV rec	Epithermal	–	JCDS	BPA 250 mg/kg	–	1/1

JCDS: JAERI-computed dosimetry system; IV rec: Patients of grade-IV recurrence or malignant transformation pathologically proven by surgical specimens; BPA: boronophenylalanine; BSH: sodium mercaptoundecahydro-closo-dodecaborate; fr: fraction

Inclusion criteria for newly diagnosed GBM were met by patients who had supratentorial unilateral tumours, located no deeper than 7 cm from the brain surface, with a Karnofsky Performance Status (KPS)  $\geq$  50, who had undergone neither previous chemotherapy or radiotherapy nor previous therapy for any other cancers, and who had no allergy to sodium borocaptate (BSH) or p-dihydroxyboryl-phenylalanine (BPA), and no previous malignancy. Patients with tumour dissemination were excluded. For recurrent cases, almost the same criteria were adopted, but a history of radiotherapy or chemotherapy was accepted. 17 GBM patients were enrolled in the clinical trial.

From the start of protocol III, newly diagnosed patients were treated with additional conventional radiotherapy. Radiotherapy was started within 2 weeks after BNCT and consisted of fractionated focal irradiation at a dose of 30 Gy delivered in 15 fractions of 2 Gy over a 3-week term. The most recently used protocol, IV, permits additional conventional radiotherapy at a dose of 40 Gy delivered in 20 fractions of 2 Gy and the concomitant use of temozolomide (TMZ) while not using BSH infusions. Protocols IIIr and IVr were treatments for recurrent or regrowing GBM patients. These are corresponding to protocols III and IV, respectively, except for previous radiochemotherapy in the inclusion criteria. Additional post-BNCT X-ray radiotherapy was abbreviated in protocols IIIr and IVr.

### Boron Compounds

Two boron compounds are used clinically in BNCT. Their chemical structures are shown in Figure 1C. First, we use sodium mercaptoundecahydro-closo-dodecaborate  $\text{Na}_2\text{B}_{10}\text{H}_{11}\text{SH}$  (BSH). BSH distributes only through the fragile tumour vessels and cannot pass the normal blood-brain barrier. Twelve hours prior to neutron irradiation, 5 g of BSH is dissolved in 500 ml normal saline and given to the patient in a 1-h intravenous infusion. The tumour/blood boron concentration ratio was not high in our patient series ( $n = 15$ ), but no adverse event related to BSH infusion was reported.

Next we tried the combined use of 2 drugs in protocol III, BSH and BPA, to improve the boron concentration of the target lesion. 90 minutes prior to neutron irradiation, dissolved BPA-fructose complex was given. Active tumour cells accumulate the BPA for protein synthesis as an amino-acid analogue. The most recent protocol IV used BPA only because we add X-ray

external irradiation after the BNCT, and this protocol may have an effect equal to that of the non-selective boron dose.

BSH was purchased from Katchem spol. (Prague, Czech Republic), and BPA was purchased from Interpharma Praha (Prague, Czech Republic) or Stella Pharma Corp (Osaka, Japan).

### Treatment-Planning System

We calculated the photon-equivalent BNCT dose by multiplying the weighting factors. We detected the thermal neutron dose by radio-activation methods with gold wire or foil placed into the operative field during craniotomy for neutron radiation. The gold wire measured radioactivity and was pulled out during or after radiation. It reflected thermal neutron fluence at the lesion. Once epithermal neutrons were introduced, BNCT was performed without craniotomy. Therefore, we cannot directly measure the neutron dose at the tumour site by gold-wire activation. To evaluate the normal and target doses a treatment planning system for BNCT was required. Previously, several systems were used for BNCT treatment planning [7, 8]. Kumada et al released the JAERI computational dosimetry system (JCDS) for clinical epithermal beam BNCT [9, 10]. The most useful point of the JCDS system was that it was manufactured by the researchers and a new version can be created for development [11, 12].

The JCDS generates a 3-D volume of data for each patient; based on the CT scan, the tissue is automatically divided into soft tissue, bone, and air. The material data of each composition have been defined by the International Commission on Radiation Units (ICRU).

The medical team defines the region of interest (ROI) of the lesions and surrounding critical organs as well as the ideal incident direction of the neutron beam. After defining the boron-related parameters including the predictive average tumour and normal boron concentrations, the relative biological effectiveness, and the limiting dose of normal surrounding tissue, the JCDS calculates the dose with a particle transport simulation – for example, using the MCNP code with the Monte-Carlo method.

The output from the JCDS can display the dose-volume histogram, the isodose contour image, which contains the boron-

related dose, and the boron-unrelated dose. The boron-unrelated dose includes the “nitrogen dose” from the interaction with nitrogen in the tissue, the “gamma-ray dose” consisting of the primary gamma-ray dose transported from the reactor core, and the secondary gamma-ray dose induced by the reaction in the tissue. The fast neutrons induce the “fast-neutron dose” by the proton recoil reaction with hydrogen nuclei.

The BNCT dose was calculated by multiplying the weighted factors to account for the radiobiological effect of the high-LET dose. There are still unsolved problems regarding the estimation of the true radiation effect because the tumour tissue is heterogeneous, and different microdistributions of boron around and in the tumour cells influence the effectiveness. The prediction of tumour boron concentration from the blood boron concentration and PET images could not reflect this heterogeneity on boron microdistributions. Hence, the tumour dose calculated here may be overestimated since there is a part of the tumour with lower boron concentration.

**Estimation of Boron Concentration and Patient Position During and After Neutron Irradiation**

The JCDS can compensate for the patient’s position with 3-D geometry position data. In our protocols, blood sampling was conducted right before and after irradiation; boron concentration of the whole blood was analysed by inductively coupled plasma-atomic emission spectroscopy (ICP-AES) and confirmed by prompt gamma ray analysis (PGA). We confirmed the patient’s final maximum normal brain dose after confirmation of the blood boron concentration and geometrical data. Later protocols permitted the performance of <sup>18</sup>F-labelled BPA positron emission tomography (PET) [40, 41] to determine the lesion-to-normal ratio of BPA-mediated <sup>10</sup>B for estimating the BPA-mediated tumour dose.

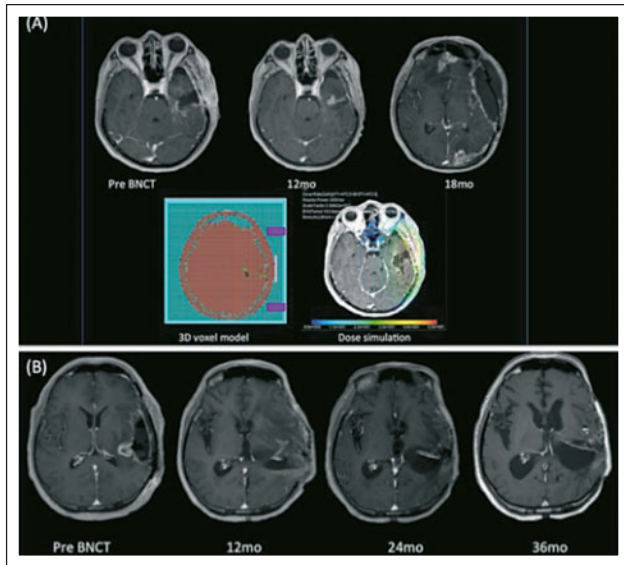
**Irradiation Set-Up (of Protocols III and IV)**

JRR-4 is located approximately 60 km from the University of Tsukuba Hospital. At the hospital, the patient is administered intravenous BSH 24 h prior to the predicted irradiation start time. An ambulance with the medical team takes the patient to JRR-4. At JRR-4, to reduce exposure, the patient position setting is done at a radiation port model, and intravenous BPA administration is initiated 1.5 h before the start of neutron irradiation. A blood sample is taken, and an electrocardiogram monitor, blood oxygen saturation monitor, and drip infusion unit are implemented. After the patient enters the irradiation room, the 3-dimensional coordinates of the patient’s head are set and recorded. By monitoring the output of the reactor and the blood

**Table 3.** Clinical characteristics of all patients who underwent BNCT.

Proto- cols	Age	Sex	Pre- BCNT KPS	Average boron blood concentration BSH	BPA	Tumour peak dose (Gy; gold wire)	PET/B ratio	Minimum tu- mour dose of CTV2.0 (Gy)	Maximum normal brain dose (Gy)	Survival (from BCNT; months)
I	55	F	80	21.3		41.3				14.1
I	46	F	90	27.9		42.7				35.3
I	38	F	100	27.6		19.8				27.6
I	64	F	40	19.7		45.6				5.6
I	51	M	90	3.6		38.7				22.3
II	41	M	100	50		22.1				10.9
II	63	F	100	47.9		28.8				22.3
III	67	F	80	32.1	16.7			10.3	11.3	34.7
III	70	F	90	24.8	21.3			21.0	14.1	26.7
III	76	F	60	50.0	15.5			13.3	8.4	8.3
III	54	F	100	34.7	17.6			16.6	11.9	27.3
III	68	M	90	36.8	14.7			19.3	11.4	26.1
III	63	M	50	32.1	18.8			10.8	11.6	7.5
III	32	F	100	46.4	15.0			21.8	11.4	79.6
III	57	F	90	21.9	19.9			7.3	11.4	42.3
IV	40	M	90		12.6			11	9.8	19.9
IVr	53	M	90		13.7			14.7	8.4	42.3

KPS: Karnofsky Performance Score; T/B ratio: tumour/blood ratio; CTV 2.0: clinical target volume 2 cm extended from the Gd-enhancing area; BPA: boronophenylalanine; BSH: sodium borocapitate



**Figure 2.** (a) Serial MRI image of the GBM patient treated with protocol IV. The scalp was unremarkable. Hair loss continued for more than 1 year. (b) Recurrent GBM patient who underwent BNCT after 60-Gy irradiation. The tumour was stable for more than 3 years.

boron concentration just before irradiation, we decide on the radiation time so that the normal surrounding-brain dose is less than 12 Gy-Eq.

### Clinical Follow-Up

All 17 patients were carefully followed up every 1–3 months by means of neurological examinations and MRI imaging. The time to progression and overall survival (OS) were determined. Adverse events were recorded with grading by the National Cancer Institute Common Toxicity Criteria Versions 2 and 3. The patients were treated with nimustine- (ACNU-) based chemotherapy as a general rule during the follow-up period. No patient had been treated with TMZ before tumour regrowth, except for one treated under protocol IV.

## ■ Results

The patients' characteristics and average boron concentrations, calculated tumour and normal brain doses are shown in Table 3. The data of 15 patients with newly diagnosed GBM were retrospectively analysed [6].

### Adverse Events

Only 2 of the newly diagnosed GBM patients suffered an acute adverse event beyond grade 2. One protocol-III patient suffered transient orbital swelling accompanied by double vision (grade 2); one of the protocol-I patients suffered post-epileptic brain swelling (grade 4) requiring surgical intervention. We had some grade-1 adverse events of redness, fever, and itching in protocols I and II.

### Boron Concentration

Patients provided as many as 7–10 blood samples before and after irradiation. Both concentrations (boron from BSH and boron from BPA) were predicted from the time course of the boron concentration curve. Average blood boron concentra-

tion from the predicted BSH and BPA concentrations was  $34.6 \pm 9.6 \mu\text{g/g}$  for BSH and  $17.4 \pm 2.4 \mu\text{g/g}$  for BPA (protocol III,  $n = 8$ ).

### Dose Estimation

In protocol I, the neutron dose was analysed with a gold radio-activation method using fine gold wires. We placed the gold wire on the surface of the brain and in the surgical cavity during craniotomy, but the spatial resolution of the measurement point was  $> 5 \text{ mm}$ . The peak dose of the treatment field is described in Table 3. The maximum normal brain dose of protocols I and II was  $29.4 \pm 6.0 \text{ Gy-Eq}$  ( $n = 7$ , range 20.1–36.0).

In protocols II–IV, as described in the treatment planning system, the boron dose and the non-boron dose were summed and converted to the equivalent dose of 2-Gy-fraction conventional radiotherapy. The maximum normal brain and skin doses were  $11.4 \pm 1.5 \text{ Gy-Eq}$ . The minimum tumour dose of the clinical target volume (CTV –2 cm) was  $15.1 \pm 5.4 \text{ Gy-Eq}$ .

### A Protocol-IV Case

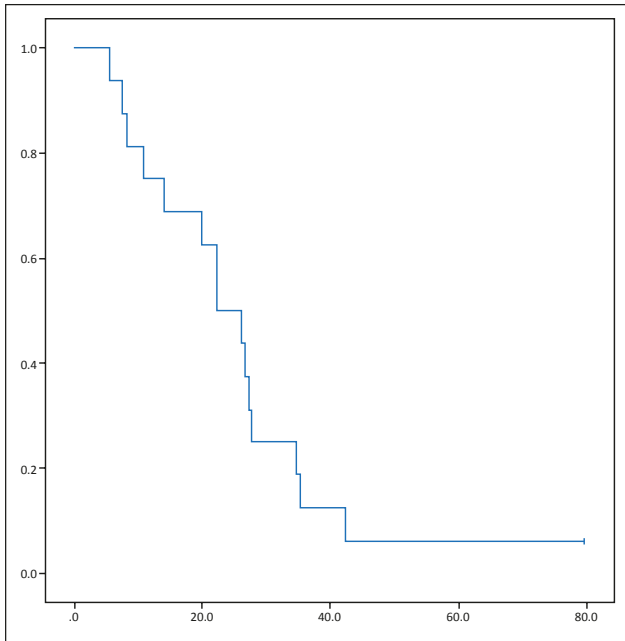
The 40-year old male patient had suffered from severe headaches due to increased intracranial pressure. Emergency left-temporal tumour removal was performed and the pathological specimen revealed a GBM. Two months after surgery, BNCT was performed. The average blood boron concentration was  $12.6 \mu\text{g/ml}$ , the maximum skin dose was 9.8 Gy, and the normal brain dose was 11.7 Gy. The minimum target (GTV + 2 cm) dose was 11.2 Gy. After BNCT, he received 40 Gy of 20 fractionated external photon irradiations instead of a BSH-induced boron dose. The serial MRI scan is shown in Figure 2. The tumour was controlled for 1 year, but outfield tumour growth resulted in his death 19.9 months after BNCT. Normal brain tissue tolerated this protocol. The effect of the protocol on the patient's scalp was unremarkable, but loss of hair remained for more than 1 year.

### Protocol-IVr Case

The 53-year old male patient had a tumour in the left-temporal lobe removed with the pathological diagnosis being GBM. At a deep part of the surgical defect, there was a residual tumour growing during postoperative radiation and concomitant temozolomide treatment. He was referred to our hospital for additional BNCT, which was performed 4 months after initial surgery, using BPA only. Average blood boron concentration was  $13.7 \mu\text{g/ml}$ , maximum skin dose was 8.4 Gy, and normal brain dose was 10.5 Gy. Minimum target (GTV + 2 cm) dose was 15.9 Gy. The serial MRI image is shown in Figure 2B. The patient underwent skin and muscle transplantation due to infection and necrosis, but more than 3 years after BNCT, the MRI image of the tumour and his performance status were stable.

### OS of Newly Diagnosed GBM

Median overall survival (mOS) of GBM patients has already been reported [34]. In our series, mOS was 22.3 months for grade-4 patients (protocols I, II, III, and IV;  $n = 16$ ). The Kaplan-Meier curve is given in Figure 3. The longest mOS was that obtained in protocol III ( $n = 8$ ) alone, which was 27.1 months.



**Figure 3.** Kaplan-Meier survival curve of BNCT-treated patients ( $n = 16$ ) with newly diagnosed glioblastoma. Median overall survival of grade-IV patients was 22.3 months.

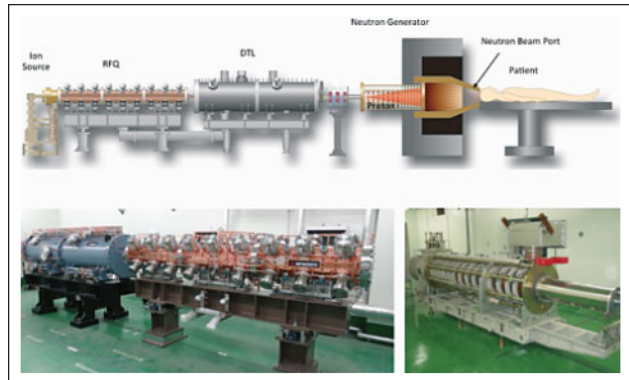
## Discussion

In our case series, we selected patients with shallow glioblastoma and KPS  $> 50$  %. During the protocol-III period, about  $\frac{1}{4}$  of the GBM patients underwent BNCT, and another  $\frac{1}{4}$  underwent proton radiotherapy. The remaining half were treated by conventional radiotherapy. We have reported that the positive effect of BNCT and proton treatment is unlikely to reflect patient selection alone in our serial case series [6], and overall survival of a particle therapy group was 24.4 months (95-% CI: 18.2–30.5 months) compared with 14.2 months (95-% CI: 10.0–18.3 months) for those treated with conventional radiotherapy. This survival difference between the conventional treatment group and the high-dose particle radiation group suggests that our case selection was appropriate.

Among the 15 selected GBM cases, we observed one long-term survivor who did not develop a recurrence over a period of  $> 5$  years. She has shown no symptoms and takes no medication. Even if a statistically significant difference is not revealed in the entire series, curing GBM is possible by choosing the cases appropriately.

GBM is the most common and invasive form of malignant glioma. The Japanese tumour registry indicates that the 1-year survival rate for GBM is 55.1 %, and the 5-year survival rate is 6.9 %. This data was collected before the approval of temozolomide, and recent data would be pre-analytical. Randomised clinical trials for GBM patients have been initiated; for example, a search of [clinicaltrials.gov](http://clinicaltrials.gov) revealed 829 trials for glioblastoma but only 45 trials with results. This illustrates that the difficulty in completing a clinical trial for GBM patients is due to the onset frequency and the limited number of patients.

Randomised controlled trials for GBM indicate that at least several hundred cases would be necessary to statistical-



**Figure 4.** Scheme of the Linac-based BNCT facility at the University of Tsukuba and photographs of the installed equipment.

ly prove the effectiveness of new chemoradiotherapy. Because reactor-based BNCT can be conducted only at a few sites around the world, it is challenging to enroll the necessary hundreds of GBM cases in order to perform randomised controlled trials and test the effectiveness of BCNT for this disease. Moreover, primary brain tumours are an “orphan disease” as the Japanese brain tumour registry revealed an annual incidence of primary brain tumours of approximately 12–15 cases per 100,000 persons and a 9.1 % rate of primal brain tumours for GBM [42].

## Other BNCT Trials for Glioblastoma

Previous BNCT clinical trials for glioma are summarised in Table 1. Kyoto University and Osaka Medical School carried out clinical trials with modern BNCT techniques. They used 100 mg/kg BSH and 700 mg/kg BPA with a 6-h infusion, and the patients also received an X-ray boost. MOS was 23.5 months following diagnosis [29, 43, 44].

Kankaanranta et al at the Helsinki University Central Hospital and the VTT Technical Research Center of Finland performed BNCT for GBM and recurrent GBM, using 290 mg/kg BPA or 450 mg/kg; the reported survival was 13.4 months and 21.9 months, respectively [27]. The European Organization for Research and Treatment of Cancer carried out a phase-I study of BSH-based BNCT (protocol #11961). They reported the toxicity of BSH-based BNCT, cerebral atrophy, and white-matter abnormalities [25, 45, 46]. A group in Sweden used 900 mg/kg BPA for a 6-h infusion. MOS for their 29 patients was 14.2 months [36, 37]. All of these clinical trials were carried out with very small numbers of patients and the patients were selected cases. It is thus difficult to compare these results with historical or standard therapy data.

## Developing Accelerator-Based BNCT

If there are many target patients, treatment throughput is very inefficient with reactor-based BNCT because of difficulties in enrolling the treatment. It is difficult to market medical equipment using a nuclear reactor in Japan, but the development of the accelerator neutron source is of greater concern. Although the accelerator neutron source presents the issues of the heat-treatment of the target and radio-activation of the facilities, a clinical treatment facility was built by Kyoto University, and a phase-I clinical trial is ongoing at the facility.

We are also developing a new neutron source. The conceptual design of the neutron generator of this Linac-based BNCT facility at the University of Tsukuba is as follows:

1. Proton energy is 8 MeV, and the average proton current is set to 10 mA.
2. A RFQ and DTL-type Linac is used as the proton accelerator of the BNCT device. Figure 4 shows a schematic drawing of the Linac-based BNCT device and photographs of the RFQ, DLT, and Klystron.
3. The design uses 0.5-mm beryllium as the neutron target material and a copper plate is located on the back-side of the thin beryllium plate as a heat sink.
4. The neutron transport device consists of a fast neutron filter; the moderator, collimator, and radiation shield were determined. In addition, a simulation calculated that the neutron generator can emit high-flux neutrons ( $> 2.0 \text{ n/cm}^2/\text{s}$ ) at the beam port.

After the entire system is installed, the intensity allows the performance of BNCT irradiation within 15 min. The entire treatment system is small enough to build in-hospital. According to the current schedule, the first clinical trial using the Linac-based BNCT facility will be performed in 2015.

There is a possibility for medical-equipment marketing with a treatment system for in-hospital facilities such as proton-beam.

### Development of Boron Agents

BPA and BSH may not be the best drugs for use in BNCT and the compound itself showed no treatment effect. Previous clinical trials revealed some adverse events such as urine crystallisation and acute renal dysfunction with BPA at a dose of 700–900 mg/kg. Safer and more effective new boron compounds are eagerly awaited but the dose remains a question; several grams of boron compounds with a one-shot intravenous administration were a stringent condition in previous trials. The most important requirement for the clinical dose is safety.

BNCT must achieve clinical usefulness in order to develop and establish effective small molecular boron compounds [47] or boronated nanoparticles using drug delivery system technology [48, 49]. We must first confirm the effectiveness of the pre-existing compounds and begin high-throughput clinical trials or approved treatment.

BNCT has the potential to be a standard treatment modality for GBM patients, but first BNCT's superiority over conventional radiotherapy must be investigated. Radiotherapy for GBM is effective at a dose of  $\geq 45 \text{ Gy}$ . High-dose treatment such as that provided by a 3-dimensional conformal beam [50], intensity-modulated radiation therapy (IMRT), or gamma knife can send a high dose to a localised lesion, but healing is not ensured [51, 52]. To assess the efficacy of cell-selective treatment for GBM, it must be determined whether boron is taken in the forefront of the invading tumour nest. Randomised control studies comparing BNCT with conventional radiation treatment are required. However, it is also necessary to lead and to develop a practical treatment system that includes a boron compound supply, an easily manageable neu-

tron source in the hospital, and a treatment-planning system that is easy for radiation oncologists to use.

### Conclusions

Our clinical trial of BNCT for glioblastoma patients showed promising survival benefits. BNCT presents a difficulty as a high-throughput treatment, and thus the studies of BNCT clinical treatment have all used small case series. To overcome these difficulties we look forward to the development of accelerator-based BNCT.

### Conflict of Interest

The authors have no conflicts of interest to report.

### References:

1. Farr LE, Sweet WH, Locksley HB, et al. Neutron capture therapy of gliomas using boron. *Trans Am Neurol Assoc* 1954; 13: 110–3.
2. Goodwin JT, Farr LE, Sweet WH, et al. Pathological study of eight patients with glioblastoma multiforme treated by neutron-capture therapy using boron 10. *Cancer* 1955; 8: 601–15.
3. Sweet WH. Early history of development of boron neutron capture therapy of tumors. *J Neurooncol* 1997; 33: 19–26.
4. Yamamoto T, Matsumura A, Yamamoto K, et al. In-phantom two-dimensional thermal neutron distribution for intraoperative boron neutron capture therapy of brain tumours. *Phys Med Biol* 2002; 47: 2387–96.
5. Yamamoto T, Matsumura A, Nakai K, et al. Current clinical results of the Tsukuba BNCT trial. *Appl Radiat Isot* 2004; 61: 1089–93.
6. Matsuda M, Yamamoto T, Kumada H, et al. Dose distribution and clinical response of glioblastoma treated with boron neutron capture therapy. *Appl Radiat Isot* 2009; 67 (Suppl): S19–S21.
7. Nigg DW. Methods for radiation dose distribution analysis and treatment planning in boron neutron capture therapy. *Int J Radiat Oncol Biol Phys* 1994; 28: 1121–34.
8. Nigg DW, Wheeler FJ, Wessol DE, et al. Computational dosimetry and treatment planning for boron neutron capture therapy. *J Neurooncol* 1997; 33: 93–104.
9. Kumada H, Yamamoto K, Yamamoto T, et al. Improvement of dose calculation accuracy for BNCT dosimetry by the multi-voxel method in JCDS. *Appl Radiat Isot* 2004; 61: 1045–50.
10. Kumada H, Yamamoto K, Matsumura A, et al. Verification of the computational dosimetry system in JAERI (JCDS) for boron neutron capture therapy. *Phys Med Biol* 2004; 49: 3353–65.
11. Kumada H, Nakamura T, Komeda M, et al. Development of a new multi-modal Monte-Carlo radiotherapy planning system. *Appl Radiat Isot* 2009; 67 (Suppl): S118–S121.
12. Kumada H, Saito K, Nakamura T, et al. Multistep Lattice-Voxel method utilizing lattice function for Monte-Carlo treatment planning with pixel based voxel model. *Appl Radiat Isot* 2011; 69: 1866–9.
13. Farr LE, Sweet WH, Robertson JS, et al. Neutron capture therapy with boron in the treatment of glioblastoma multiforme. *Am J Roentgenol Radium Ther Nucl Med* 1954; 71: 279–93.
14. Slatkin DN. A history of boron neutron capture therapy of brain tumours. *Postulation of a brain radiation dose tolerance limit. Brain* 1991; 114: 1609–29.
15. Asbury AK, Ojemann RG, Nielsen SL, et al. Neuropathologic study of fourteen cases of malignant brain tumor treated by boron-10 slow neutron capture radiation. *J Neuropathol Exp Neurol* 1972; 31: 278–303.
16. Sauerwein W. Principles and history of neutron capture therapy. *Strahlenther Onkol* 1993; 169: 1–6.
17. Hatanaka H. Experience of boron-neutron capture therapy for malignant brain tumours – with special reference to the problems of postoperative CT follow-ups. *Acta Neurochir Suppl* 1988; 42: 187–92.
18. Hatanaka H, Amano K, Sano K, et al. [Boron-10-slow neutron capture therapy for brain tumors (author's transl)]. *No Shinkei Geka* 1974; 2: 7–16.
19. Coderre JA, Turcotte JC, Riley KJ, et al. Boron neutron capture therapy: cellular targeting of high linear energy transfer radiation. *Technol Cancer Res Treatment* 2003; 2: 355–75.
20. Chanana AD, Capala J, Chadha M, et al. Boron neutron capture therapy for glioblastoma multiforme: interim results from the phase I/II dose-escalation studies. *Neurosurgery* 1999; 44: 1182–92.
21. Diaz AZ. Assessment of the results from the phase I/II boron neutron capture therapy trials at the Brookhaven National Laboratory from a clinician's point of view. *J Neurooncol* 2003; 62: 101–9.
22. Chadha M, Capala J, Coderre JA, et al. Boron neutron-capture therapy (BNCT) for glioblastoma multiforme (GBM) using the epithermal neutron beam at the Brookhaven National Laboratory. *Int J Radiat Oncol Biol Phys* 1998; 40: 829–34.
23. Palmer MR, Goorley JT, Kiger WS, et al. Treatment planning and dosimetry for the Harvard-MIT phase I clinical trial of cranial neutron capture therapy. *Int J Radiat Oncol Biol Phys* 2002; 53: 1361–79.
24. Busse PM, Harling OK, Palmer MR, et al. A critical examination of the results from the Harvard-MIT NCT program phase I clinical trial of neutron capture therapy for intracranial disease. *J Neurooncol* 2003; 62: 111–21.
25. Vos MJ, Turowski B, Zanella FE, et al. Radiologic findings in patients treated with boron neutron capture therapy for glioblastoma multiforme within EORTC trial 11961. *Int J Radiat Oncol Biol Phys* 2005; 61: 392–9.
26. Wittig A, Moss RL, Stecher-Rasmussen F, et al. Neutron activation of patients following boron neutron capture therapy of brain tumors at the high flux reactor (HFR) Petten



- (EORTC Trials 11961 and 11011). *Strahlenther Onkol* 2005; 181: 774–82.
27. Kankaanranta L, Seppala T, Koivunoro H, et al. L-boronophenylalanine-mediated boron neutron capture therapy for malignant glioma progressing after external beam radiation therapy: a phase I study. *Int J Radiat Oncol Biol Phys* 2011; 80: 369–76.
28. Joensuu H, Kankaanranta L, Seppala T, et al. Boron neutron capture therapy of brain tumors: clinical trials at the Finnish facility using boronophenylalanine. *J Neurooncol* 2003; 62: 123–34.
29. Kawabata S, Miyatake S, Hiramatsu R, et al. Phase II clinical study of boron neutron capture therapy combined with X-ray radiotherapy/temozolomide in patients with newly diagnosed glioblastoma multiforme – study design and current status report. *Appl Radiat Isot* 2011; 69: 1796–9.
30. Miyatake S, Kawabata S, Kajimoto Y, et al. Modified boron neutron capture therapy for malignant gliomas performed using epithermal neutron and two boron compounds with different accumulation mechanisms: an efficacy study based on findings on neuroimaging. *J Neurosurg* 2005; 103: 1000–9.
31. Miyatake S, Kawabata S, Yokoyama K, et al. Survival benefit of Boron neutron capture therapy for recurrent malignant gliomas. *J Neurooncol* 2009; 91: 199–206.
32. Kageji T, Mizobuchi Y, Nagahiro S, et al. Clinical results of boron neutron capture therapy (BNCT) for glioblastoma. *Appl Radiat Isot* 2011; 69: 1823–5.
33. Kageji T, Nagahiro S, Matsuzaki K, et al. Boron neutron capture therapy using mixed epithermal and thermal neutron beams in patients with malignant glioma—correlation between radiation dose and radiation injury and clinical outcome. *Int J Radiat Oncol Biol Phys* 2006; 65: 1446–55.
34. Yamamoto T, Nakai K, Kageji T, et al. Boron neutron capture therapy for newly diagnosed glioblastoma. *Radiother Oncol* 2009; 91: 80–4.
35. Yamamoto T, Nakai K, Nariai T, et al. The status of Tsukuba BNCT trial: BPA-based boron neutron capture therapy combined with X-ray irradiation. *Appl Radiat Isot* 2011; 69: 1817–8.
36. Capala J, Stenstam BH, Skold K, et al. Boron neutron capture therapy for glioblastoma multiforme: clinical studies in Sweden. *J Neurooncology* 2003; 62: 135–44.
37. Henriksson R, Capala J, Michanek A, et al.; Swedish Brain Tumour Study Group. Boron neutron capture therapy (BNCT) for glioblastoma multiforme: a phase II study evaluating a prolonged high-dose of boronophenylalanine (BPA). *Radiother Oncol* 2008; 88: 183–91.
38. Skold K, H-Stenstam B, Diaz AZ, et al. Boron Neutron Capture Therapy for glioblastoma multiforme: advantage of prolonged infusion of BPA-f. *Acta Neurol Scand* 2010; 122: 58–62.
39. Pellettieri L, H-Stenstam B, Rezaei A, et al. An investigation of boron neutron capture therapy for recurrent glioblastoma multiforme. *Acta Neurol Scand* 2008; 117: 191–7.
40. Imahori Y, Ueda S, Ohmori Y, et al. Fluorine-18-labeled fluoroboronophenylalanine PET in patients with glioma. *J Nucl Med* 1998; 39: 325–33.
41. Nariai T, Ishiwata K, Kimura Y, et al. PET pharmacokinetic analysis to estimate boron concentration in tumor and brain as a guide to plan BNCT for malignant cerebral glioma. *Appl Radiat Isot* 2009; 67 (Suppl): S348–S350.
42. Report of Brain Tumor Registry of Japan (1984–2000). *Neurol Med Chir* 2009; 49 (Suppl): PS1–PS96.
43. Kawabata S, Miyatake S, Nonoguchi N, et al. Survival benefit from boron neutron capture therapy for the newly diagnosed glioblastoma patients. *Appl Radiat Isot* 2009; 67 (Suppl): S15–S18.
44. Miyatake S, Kawabata S, Yokoyama K, et al. Survival benefit of boron neutron capture therapy for recurrent malignant gliomas. *Appl Radiat Isot* 2009; 67 (Suppl): S22–S24.
45. Hideghety K, Sauerwein W, Haselsberger K, et al. Postoperative treatment of glioblastoma with BNCT at the petten irradiation facility (EORTC protocol 11,961). *Strahlenther Onkol* 1999; 175 (Suppl 2): 111–4.
46. Sauerwein W, Zurlo A; EORTC Boron Neutron Capture Therapy Group. The EORTC Boron Neutron Capture Therapy (BNCT) Group: achievements and future projects. *Eur J Cancer* 2002; 38 (Suppl 4): S31–S34.
47. Rosenthal MA, Kavar B, Hill JS, et al. Phase I and pharmacokinetic study of photodynamic therapy for high-grade gliomas using a novel boronated porphyrin. *J Clin Oncol* 2001; 19: 519–24.
48. Wu G, Barth RF, Yang W, et al. Boron containing macromolecules and nanovehicles as delivery agents for neutron capture therapy. *Anticancer Agents Med Chem* 2006; 6: 167–84.
49. Kueffer PJ, Maitz CA, Khan AA, et al. Boron neutron capture therapy demonstrated in mice bearing EMT6 tumors following selective delivery of boron by rationally designed liposomes. *Proc Natl Acad Sci USA* 2013; 110: 6512–7.
50. Tanaka M, Ino Y, Nakagawa K, et al. High-dose conformal radiotherapy for supratentorial malignant glioma: a historical comparison. *Lancet Oncol* 2005; 6: 953–60.
51. Jastaniyah N, Murtha A, Pervez N, et al. Phase I study of hypofractionated intensity modulated radiation therapy with concurrent and adjuvant temozolomide in patients with glioblastoma multiforme. *Radiat Oncol* 2013; 8: 38.
52. Park KJ, Kano H, Iyer A, et al. Salvage gamma knife stereotactic radiosurgery followed by bevacizumab for recurrent glioblastoma multiforme: a case-control study. *J Neurooncol* 2012; 107: 323–33.