

# Boron neutron capture therapy for brain tumors

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**Abstract:** Boron neutron capture therapy (BNCT) is a unique method that can provide the delivery of tumor cell-selective high-linear energy transfer (LET) particle radiotherapy to tumor mass and the microscopic invasion while avoiding radiation damage to the surrounding normal brain tissue. The rationale of BNCT is based on the nuclear interaction of  $^{10}\text{B}$  with thermal neutrons with the release of high LET  $\alpha$  and  $^7\text{Li}$  particles through the boron neutron capture reaction,  $^{10}\text{B}(n, \alpha) ^7\text{Li}$ . The very short path length ( $<9 \mu\text{m}$ ) of  $\alpha$ -particles and  $^7\text{Li}$  enables high-LET irradiation of tumor cells without undesirable damage to  $^{10}\text{B}$ -unloaded normal cells. Eight non-randomized prospective external beam BNCT trials for glioblastoma (GBM) have been performed over the past 15 years using two available boron drugs and neutron beams at nuclear reactors. The reported median time to progression and the median survival time are 6-12 and 12-27 mos, respectively. Optimization of dosage and boron delivery agents, the combined use of different boron agents, the combination of BNCT with other therapeutic modalities, and the development of in-hospital accelerator-based neutron sources are underway for the improvement of BNCT. In light of the existing clinical reports, there is a clear need for more evidence-based data.

**Key Words:** Boron neutron capture therapy; glioblastoma; accelerator



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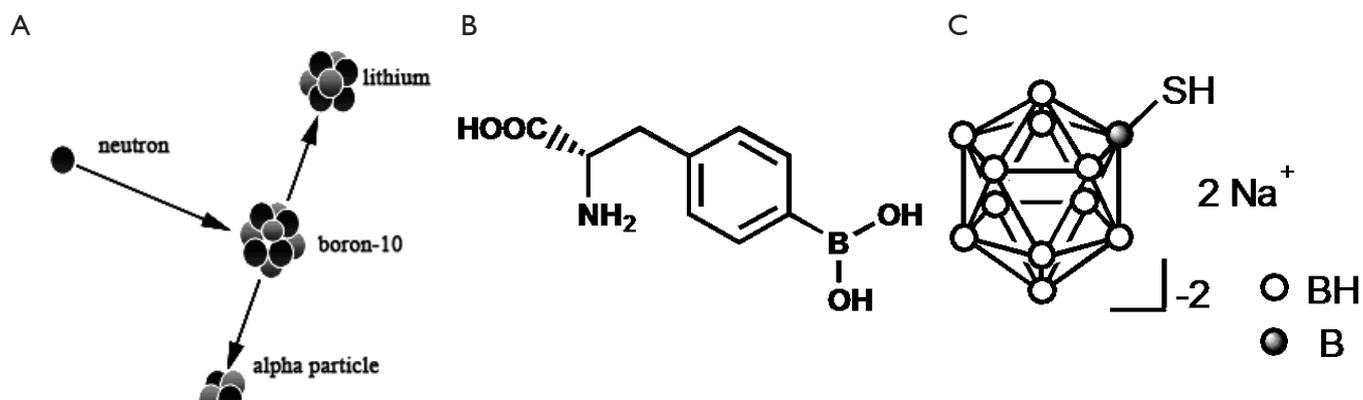
## Introduction

Glioblastoma (GBM) is a common malignant brain tumor in adults, and many recur within several months and show fatal progression within 2 years after the initial treatment. Extensive resection of the contrast-enhancing part of a tumor under image-guided surgery using fluorescence with 5-aminolevulinic acid, neuronavigation, and intraoperative magnetic resonance imaging (MRI) is shown to be beneficial for prolongation of the post-operative survival time (1,2). Aggressive cyto-reductive surgery is not indicated for the tumor in the eloquent brain. Invading cells are evident at distances of 2 to 3 cm or even further from the main tumor mass of GBM, which can be clinically identified by the contrast enhancement area on a magnetic resonance image. Thus, post-operative adjuvant therapies are essential for the treatment of post-surgical residual tumor mass and microscopic invading tumor cells in the patients with GBM.

Among several chemotherapeutic agents for malignant glioma (3,4), the effectiveness of temozolomide or

carmustine wafers has been shown. For example, the EORTC clinical trial provided Class I evidence that the concomitant and adjuvant use of temozolomide with the conventional radiotherapy leads to a modest but significant survival advantage (median survival time, or MST: 14.6 mos) compared to the conventional radiotherapy alone (MST 12.1 mos), approximately with 25% of the patients surviving longer than 24 mos (5).

Two prospective studies provided Class II evidence and also showed modest benefits of carmustine wafers for GBM patients (4). In the report of Westphal *et al.* (6), a subanalysis of 207 GBM patients showed that the carmustine wafer group had a longer mean survival (13.5 mos) than the placebo group (11.4 mos). In a study by Valtonen *et al.* (7), regarding the survival of the 27 GBM patients among the whole series of 32 patients, the group that received carmustine wafers had a longer mean survival (53.3 wks) than the placebo wafer group (39.9 wks). Because of the limited benefits produced by standard (conventional) radiotherapy and chemotherapy



**Figure 1** Neutron capture reaction of  $^{10}\text{B}$  (A) and currently available boron delivery agents: boronophenylalanine *p*-dihydroxyboryl-phenylalanine (BPA, B) and borocaptate sodium sulfhydryl borane  $\text{Na}_2\text{B}_{12}\text{H}_{11}\text{SH}$  (BSH, C)

to date, there has been also significant interest in new entity of radiotherapy and targeted molecular agents for the treatment of GBM.

Dose escalation studies using conventional X-ray fractionation, stereotactic radiosurgery, fractionated proton beam radiation, or other conformal radiotherapies have shown median survival times which vary from 9.5 to 26 mos (8,9). These studies and their failure analyses imply that at least 90 Gy must be delivered to achieve local control of GBM. Such a high-dose of radiation exceeds the accepted tolerance of normal brain tissue. Thus, high-dose radiation must be delivered with the upmost selectivity for tumor cells, to minimize radiation damage to the surrounding normal brain. Tumor-cell selectivity at the microscopic level is thus desirable. BNCT has been indicated primarily for GBM because of the theoretical selective sterilization of microscopic invading cells in the brain.

### Boron neutron capture therapy (BNCT)

Boron neutron capture therapy (BNCT) has been proposed to provide tumor cell-selective high-linear energy transfer particle radiotherapy. The nuclear reaction between boron-10 ( $^{10}\text{B}$ ) and thermal neutrons releases high LET  $\alpha$  and  $^7\text{Li}$  particles through the boron neutron capture reaction,  $^{10}\text{B}(n, \alpha)^7\text{Li}$  (Figure 1). The very short path length ( $<9 \mu\text{m}$ ) of  $\alpha$ -particles and  $^7\text{Li}$  enables high-LET irradiation of  $^{10}\text{B}$ -loaded tumor cells, minimizing undesirable damage to  $^{10}\text{B}$ -unloaded normal cells. The effectiveness of BNCT is highly dependent on the amount of these particles and the selectivity of the boron compound in tumor cells. In BNCT clinical study, the minimum tumor dose of gross tumor

volume (GTV) was around 30 Gy (10).

Although low-energy thermal neutrons ( $<0.53 \text{ eV}$ ) are captured most efficiently by  $^{10}\text{B}$  nuclei, the shallow penetration limits their usefulness. For external beam BNCT, it is essential to use epithermal neutrons, which lose energy during the penetration of normal tissue (e.g., skin, cranium) and convert to thermal neutrons. Most commonly in BNCT for brain tumors, epithermal neutron beam irradiation is performed at a research reactor, and in a single fraction (Figure 2).

To deliver  $^{10}\text{B}$ , two boron drugs, *p*-dihydroxyboryl-phenylalanine (BPA) and sulfhydryl borane  $\text{Na}_2\text{B}_{12}\text{H}_{11}\text{SH}$  (BSH), are currently available for BNCT clinical studies (Figure 1). Positron emission tomography (PET) is used to estimate the  $^{10}\text{B}$  concentration and to determine the eligibility of a patient for BNCT, by calculating the lesion-to-normal (L/N) ratio of  $^{18}\text{F}$ -labeled BPA. The uptake in  $^{11}\text{C}$ -methionine-PET, which has been more extensively studied for cancer diagnoses, is shown to have a linear correlation with that of  $^{18}\text{F}$ -BPA-PET (Figure 3), indicating the potential application of  $^{11}\text{C}$ -methionine-PET for BNCT dose planning and candidate selection (11). Before neutron irradiation, boron compounds (BSH and/or BPA) are administered intravenously, and then blood samples are drawn serially after the intravenous injection of the boron agent to measure their level in the blood.

### Neutron source for BNCT: from reactor to accelerator

The major issues in BNCT research concern the neutron sources, boron compounds, and clinical applications.

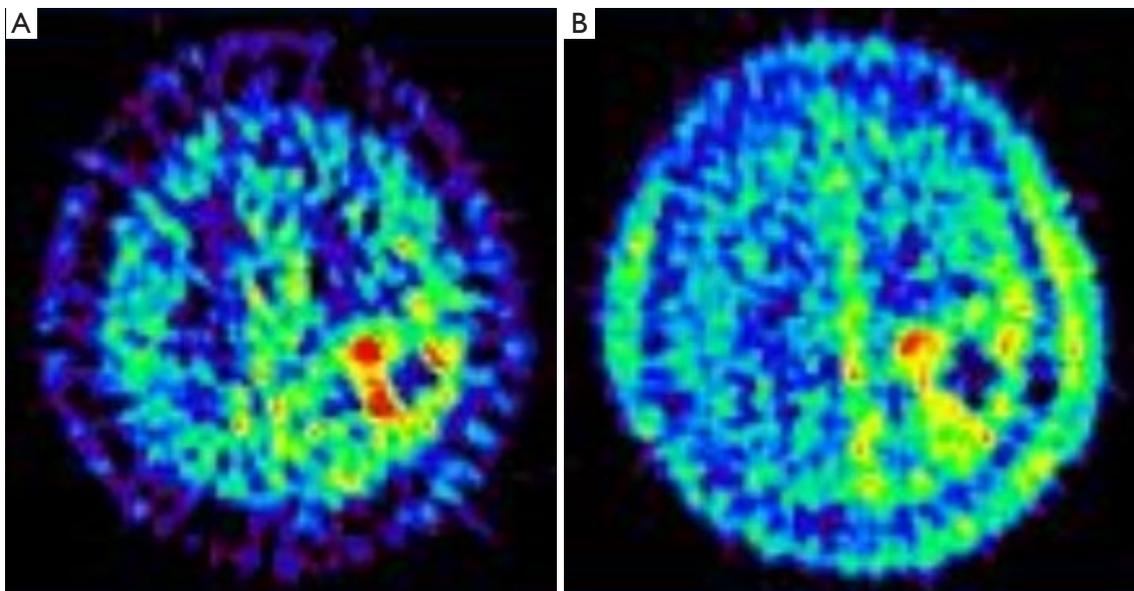


**Figure 2** Neutron irradiation room and head positioning at Japan Research Reactor No. 4 (JRR-4). The patient's head position is fixed under the laser-guided positioning device in the neutron irradiation room. The relation between the beam direction and the patient's head position is also shown

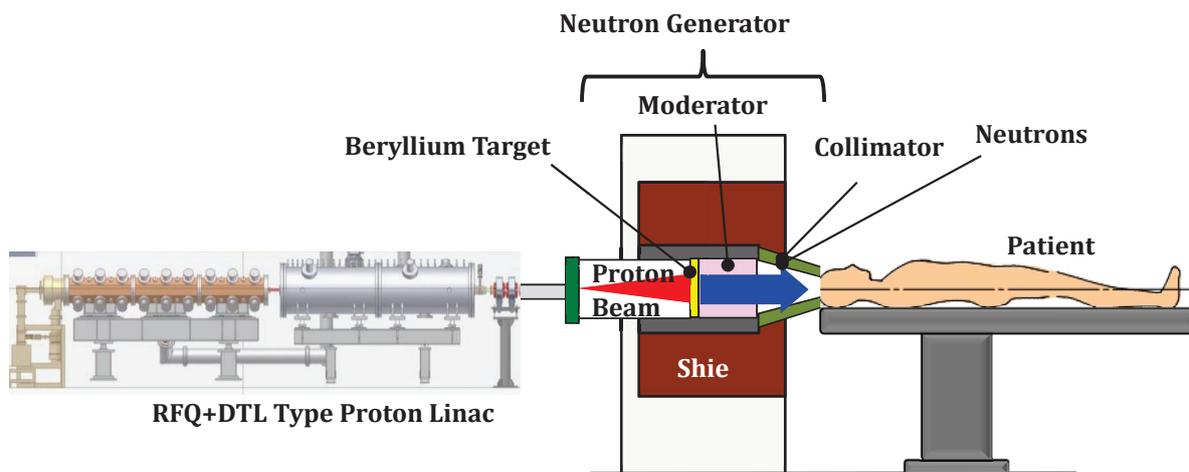
BNCT research has been conducted for more than 60 years using nuclear research reactors. The first clinical studies for malignant brain tumors were performed at Brookhaven National Laboratory (BNL) and Massachusetts Institute of Technology (MIT) in 1950s and 1960s. In these early BNCT trials, low-energy thermal neutron beams were used for irradiation; however, because of shallow penetration, BNCT with thermal neutrons required craniotomy, to allow the neutrons to reach deeper regions of the brain.

In the 1990s, external beam BNCT using higher-energy (0.53-10 keV) epithermal neutrons was initiated using the Brookhaven Medical Research Reactor (BMRR) at BNL and a High Flux Reactor (HFR) at Petten, the Netherlands. This extended the therapeutic range deeper into the brain from 4 to 8 cm, and allowed the application of nonoperative external beam irradiation (12).

A typical research reactor for BNCT has only one irradiation port fixed in the side wall of the irradiation room, and this limits achieving desirable dose distribution compared to the current multiple field irradiation or conformation radiotherapy. The locations of research reactors usually require the transfer of the patient from a hospital, and this is unusually not possible until a few weeks after surgery. In Japan, the availability of machine time is limited by research projects, maintenance, and inspections. To resolve these nuclear reactor limitations, in-hospital accelerator-based neutron sources have been developed



**Figure 3**  $^{11}\text{C}$ -Methionine-PET (A) and  $^{18}\text{F}$ -BPA-PET (B) of a left frontal glioblastoma (GBM). Similar uptake is shown at the posteromedial wall of the surgical cavity



**Figure 4** Schematic drawing of the linac-based beryllium target accelerator BNCT system which is under development in Tsukuba, Japan. Reduced proton energy (8 MeV) and current (10 mA) of a radio-frequency quadrupole (RFQ) linac and a drift-tube-linac (DTL) as proton accelerators minimize activation of the target and other materials of the neutron generator device, but are high enough to generate an epithermal neutron flux  $>1.0^9$  n/cm<sup>2</sup>/s. A schematic drawing of the linac-based BNCT device is also shown

and are now providing neutron beams for clinical study of BNCT. The accelerator BNCT system consists of a proton accelerator, target, moderator, collimator, and irradiation room, and neutrons are provided by the reaction of the target material (Be, Li, etc.) and the accelerated protons (Figure 4). The first clinical trial of BNCT for brain tumors using the beryllium target accelerator system was initiated at KURRI in Japan in late 2012.

### Boron compound and delivery system

A variety of boron delivery agents have been investigated to date, including amino acids, porphyrins, nanoparticles, polyamines, biochemical precursors, DNA-binding agents, sugars, antisense agents, peptides, proteins, monoclonal antibodies, and liposomes. However, there are only two boron delivery agents available for clinical BNCT trials for malignant glioma: <sup>10</sup>B-enriched BPA and BSH (Figure 1). <sup>10</sup>B constructs 20% of natural nonradioactive boron and has high efficiency in capturing thermal neutrons to generate boron neutron capture reaction, <sup>10</sup>B(n, α) <sup>7</sup>Li (13). Successful BNCT is dependent on the selective accumulation and absolute level of <sup>10</sup>B atoms in tumor cells.

These boron delivery agents must be as safe as glucose, and drug administration of gram-order is commonly needed to achieve a high enough intracellular boron level to sterilize tumor cells. A boron delivery agent should be non-toxic at the clinically effective doses, achieve at least

10-30 μg <sup>10</sup>B/g of tumor, have high tumor/brain and tumor/blood concentration ratios, and show rapid clearance from the blood circulation and normal tissues (but persist in the tumor). They should also be water soluble and chemically stable (14).

BPA has structural characteristics similar to those of a melanin precursor, and promising clinical results were shown in a pilot study of BNCT for skin melanoma (14). BPA is usually administered intravenously as a soluble fructose complex, BPA-F, at doses ranging from 250 to 900 mg BPA/kg. BPA can penetrate across the blood-brain barrier into the normal brain, and is actively transported through the tumor cell membrane due to the elevated rate of amino acid transport in proliferating cells. Although the uptake of BPA depends highly on individual tumors, high tumor-to-normal-BPA-uptake ratios (2.1-7.1) were demonstrated in an <sup>18</sup>F-BPA-PET study of newly diagnosed GBMs (15).

BSH biodistribution studies have suggested that BSH is distributed through passive diffusion from the blood to tumor tissues via the disrupted blood-brain barrier. The boron concentration in the normal brain with an intact blood-brain barrier remains minimal, whereas the tumor <sup>10</sup>B concentration is related to both the tumor vessel density and the blood <sup>10</sup>B level. Tumor-to-blood boron concentration ratios ranging from 0.5 to 1.0 have been reported in human patients treated with BSH-mediated BNCT (12). Vascular irritation, fever, skin reaction (erythema), and peripheral

vasoconstriction have been reported as probable adverse effects of BSH injection (10). Japanese clinical trials have used a combination of BPA and BSH based on experimental data which showed these different compounds accumulate in different subpopulations of tumor cells (12).

### Clinical studies of BNCT

In a clinical trial using epithermal neutrons at the BNL in which 53 GBMs were irradiated to evaluate the safety and effectiveness of external beam BNCT (16,17), no major adverse events were found following the 2-h intravenous injection of BPA-F at a dose of 250 to 330 mg/kg. However, patients who received 330 mg/kg BPA showed precipitates in the urine. MST following one, two and three field (one fraction each) BNCT were 14.8, 12.1 and 11.9 mos, respectively. Two of the seven subjects received an average brain dose (ABD) of 8 Gy-Eq or above, using three fields, and had grade 3 CNS toxicity. An ABD of 6.2 Gy-Eq was associated with 50% incidence of somnolence. Other grade 3 radiation toxicity was ototoxicity (17,18).

In the clinical trial at Harvard/MIT (19), no adverse event was found in relation to the intravenous injection of 250 mg/kg over 1 h, 300 mg/kg over 1.5 h, and 350 mg/kg over 1.5 h. The tumors with volumes <60 cm<sup>3</sup> and >60 cm<sup>3</sup> were associated with a 19% and 67% incidence of developing grade 3 or higher toxicity, respectively. Experimental data suggest that a longer infusion time up to 6 hours may improve the homogeneity of boron accumulation in tumors in BPA-mediated BNCT (20,21). This method was applied to the phase II clinical trial at the Studsvik BNCT facility for 29 patients suffering from GBM, who received 900 mg/kg BPA-F in a 6-h infusion, where the average boron concentration in the blood was 24.7 µg/g (22,23). Four patients developed grade 3-4 toxic events including epileptic seizures, hematuria, thrombosis, and erythema. These events except for seizures may relate to BPA administration. The median progression free survival and median MST were 5.8 and 17.7 mos, respectively.

The Finnish phase I/II trial showed that the BPA dose level of 450 mg/kg was the optimal dose for further BNCT studies of newly diagnosed GBM (24,25). In that study, 290 mg/kg of BPA was infused over 2 h in the first 12 patients suffering from GBM using two fields, and the BPA dose to subsequent patients was escalated from 330 mg/kg (n=1) to 360 mg/kg (n=3), 400 mg/kg (n=3), 450 mg/kg (n=3), and 500 mg/kg (n=8). The maximum tolerated dose was reached at the BPA dose level of 500 mg/kg, where

grade 3 (n=2) and grade 4 (n=1) CNS toxicity was found. Kankaanranta *et al.* (26) also reported a phase I dose escalation study for recurrent malignant glioma after initial treatment using X-ray fractionated radiotherapy at a dose of 50 to 61Gy, and they recommended up to 400 mg/kg L-BPA as a 2-h infusion. The MST values for the dose groups of 290, 330/360, 400, 450, and 500 mg BPA/kg were 13.4, 11.0, 16.9, 21.9 and 14.7 mos, respectively. The other studies' protocol using long-term infusions showed that the median time from BNCT treatment to tumor progression was 5.8 mos, and the MST after BNCT was 14.2 mos (22,23).

The longer perfusion method was also employed in a trial at Osaka Medical College (700 mg/kg for 6 h) (15). Experimental data also suggest that the combination of BNCT and photon radiation leads to significant gains in survival (21). In the trial conducted at Osaka Medical College, the first 10 patients suffering from GBM were administered 100 mg/kg of BSH and 250 mg/kg of BPA in a 1-h infusion (protocol 1), and the latter 11 patients were administered 100 mg/kg of BSH and 700 mg/kg of BPA in a 6-h infusion (protocol 2). A 2 Gy daily fraction of X-ray irradiation was added in protocol 2 for a total dose of 20 to 30 Gy. The MST for all patients and for protocol 2 patients were 15.6 and 23.5 mos, respectively (15).

In a trial at the University of Tsukuba and Tokushima University at Japan Research Reactor No. 4 (JRR-4) of the Japan Atomic Energy Agency (JAEA) (10), the low dose (250 mg/kg) of BPA was administered over 1 h and 5 g BSH /kg was infused over 1 h in 8 patients with a single irradiation field. These patients received additional photon radiation defining the signal abnormality in T2-weighted MRI after the completion of BNCT. The MST and the time to progression were 27.1 and 11.9 mos, respectively. The 1-year and 2-year survival rates were 87.5% and 62.5%, respectively. This small number of patients showed the most favorable outcome with BNCT to date and treatment was well tolerated without severe acute or subacute adverse events. Four of 15 patients showed delayed radiation necrosis and median survival time of 4 patients including 1 alive patient was 43.4 mos (15.1-76.0). Although it is not certain whether the additional photon irradiation has a role in the clinical response to BNCT, the survival of the small cohort seemed to be favorable.

The clinical studies for newly diagnosed GBM revealed that the median time to progression varies from 6 to 12 mos and the MST varies from 12 to 27 mos after BNCT as an initial treatment (10). More clinical data are needed to confirm

the effectiveness of this modality, although the existing results appear promising, and warrant further investigation. Future areas of research include clinical applications, the development of new boron delivery agents, and accelerator neutron sources.

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### Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.3978/j.issn.2218-676X.2013.04.11>). KT serves as an unpaid editorial board member of *Translational Cancer Research*. The other authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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